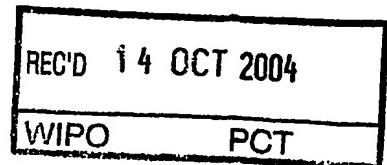


PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen



**Intyg
Certificate**

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande AstraZeneca AB, Södertälje SE
Applicant (s)

(21) Patentansökningsnummer 0302570-7
Patent application number

(86) Ingivningsdatum 2003-09-26
Date of filing

Stockholm, 2004-08-03

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund
Hjördis Segerlund

Avgift
Fee 170:-

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY

BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF

5 BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiavascular disorders.

2. Discussion of Relevant Technology

15 Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB₁ receptor, CB₂ receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

20 While CB₁ receptor agonists, such as Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and anandamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB₁ receptors located in CNS. There are lines of evidence, however, suggesting that CB₁ agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

25 Therefore, there is a need for new CB₁ receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE INVENTION

The present invention provides CB₁ receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

Definitions

- 5 Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by reference herein for its exemplary chemical structure names and rules on naming chemical structures.
- 10 "CB₁/CB₂ receptors" means CB₁ and/or CB₂ receptors.
The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.
The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.
- 15 The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.
The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" generally includes both saturated alkyl and unsaturated alkyl.
The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serve to link two structures together.
- 20 25 The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.
The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.
- 30 The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

- 5 The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

- 10 The term "aryl" used alone or as suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring.

The term "non-aromatic group" or "non-aromatic" used alone, as suffix or as prefix, refers to a chemical group or radical that does not contain a ring having aromatic character (e.g., $4n + 2$ delocalized electrons).

- 15 The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

- 20 The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

25 The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

- 30 The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-

containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

5 The term "heterocyclyl" used alone or as a suffix or prefix, refers a radical derived from a heterocycle by removing at least one hydrogen from a carbon of a ring of the heterocycle.

10 The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

15 The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on a carbon of an aromatic ring of the heterocyclyl.

20 The term "heterocycloalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

25 The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

25 A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 30 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more

- 5 C₁₋₁₂hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₁₂hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

- 10 The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

- 15 The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

- 20 Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, 25 piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

- 25 In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, 5 phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and 10 quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, 15 diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-20 pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, 25 pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including 30 both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl,

xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl,

5 benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocycls described above, heterocycl includes polycyclic heterocycls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms

10 common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy,

15 cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar', wherein -Ar' is a heteroaryl.

20 The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula -NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means -C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include,

25 for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

30 "RT" or "rt" means room temperature.

A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

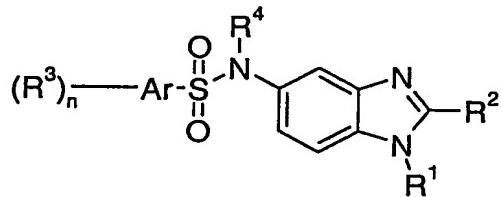
When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

5 "Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom generally adopts an sp^3 atomic orbital hybridization.

10 "Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a sp or sp^2 atomic orbital hybridization.

15 Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 is selected from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{R}^5\text{R}^6\text{N-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{O-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{C(=O)N(-R}^6\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{CS(=O)}_2\text{N(-R}^6\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NC(=O)N(-R}^7\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{N(R}^7\text{)-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{1-10}\text{hydrocarbyl amino}$, $\text{R}^5\text{R}^6\text{N-}$, $\text{R}^5\text{O-}$, $\text{R}^5\text{C(=O)N(-R}^6\text{)-}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{-}$, $\text{R}^5\text{CS(=O)}_2\text{N(-R}^6\text{)-}$, $\text{R}^5\text{R}^6\text{NC(=O)N(-R}^7\text{)-}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{N(R}^7\text{)-}$, $\text{C}_{6-10}\text{aryl}$, $\text{C}_{6-10}\text{aryl-C(=O)-}$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-6}\text{heterocyclyl}$ and $\text{C}_{3-6}\text{heterocyclyl-C(=O)-}$; wherein said $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$,

C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl,
C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino,
C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or
C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more

5 groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy,
and -NR⁵R⁶;

R² is selected from C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein

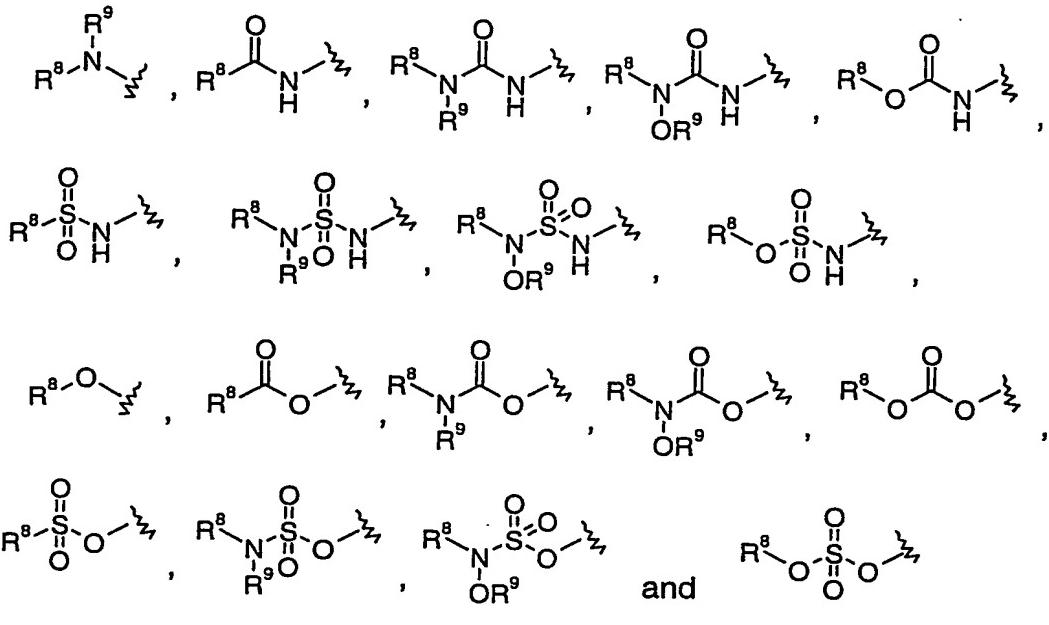
10 said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl,
C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋sheteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally
substituted by one or more groups selected from halogen, cyano, nitro, methoxy,
ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

15 wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl,
C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵,
R⁶ or R⁷ forms a portion of a ring;

Ar is selected from C₆₋₁₀aryl and C₃₋₅heteroaryl;

n is selected from 0, 1, 2 and 3;

20 each of R³ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl,
C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl,
C₃₋₆heterocycloalkyl optionally substituted with one or more groups selected from
C₁₋₆alkyl, halogen, amino and C₁₋₆alkoxy,



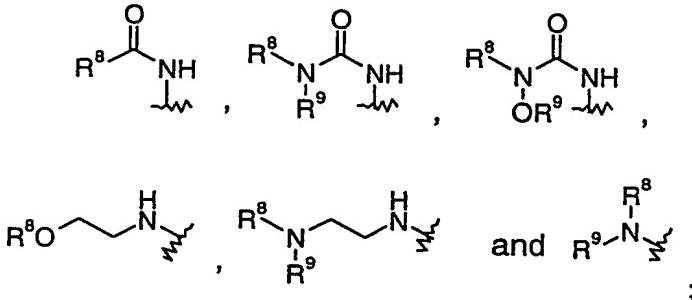
each of R^8 and R^9 is independently selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclcyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, and a divalent C_{1-6} group that together

- 5 with another divalent group selected from R^8 and R^9 forms a portion of a ring, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclcyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, or divalent C_{1-6} group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$; and
- 10 R^4 is selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, and C_{4-8} cycloalkenyl- C_{1-6} alkyl.

Particularly, the compounds of the present invention are those of formula I, wherein

- 15 R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

- R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_4-6 cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , and phenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl,
- 5 C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , and phenyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;
- wherein R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, and a divalent C_{1-6} alkylene that together with another divalent R^5 or R^6 and optionally
- 10 a heteroatom forms a portion of a ring;
- Ar is selected from phenyl and C_{3-5} heteroaryl;
- n is selected from 0, 1 and 2;
- each of R^3 is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl optionally substituted with one or more groups
- 15 selected from C_{1-6} alkyl and halogen,



- each of R^8 and R^9 is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl are optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^{10}R^{11}$; and
- R^4 , R^{10} and R^{11} are independently selected from $-H$ and C_{1-3} alkyl.

- 25 More particularly, the compounds of the present invention are those of formula I,

wherein R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl,

C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_3 -

α -heterocycloalkyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen,

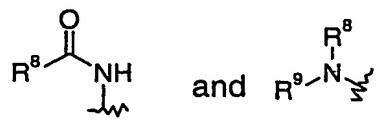
5 methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

10 Ar is selected from phenyl and C_{3-5} heteroaryl and

n is selected from 0, 1 and 2;

each of R^3 is independently selected from -H, C_{1-3} alkyl, C_{3-6} heterocycloalkyl



optionally substituted with one or more C_{1-6} alkyl,

wherein said C_{3-6} heterocycloalkyl contain at least one nitrogen ring atom and
15 the radical of C_{3-6} heterocycloalkyl is located on the at least one nitrogen ring atom,
and wherein each of R^8 and R^9 is independently selected from -H, C_{1-6} alkyl,
morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl, wherein said
 C_{1-6} alkyl, morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl are
optionally substituted by one or more groups selected from halogen, methoxy, ethoxy,
20 methyl, ethyl, hydroxy and $-NR^5R^6$; and
 R^4 , R^5 and R^6 are independently selected from -H and C_{1-3} alkyl.

Most particularly, the compounds of the present invention are those of formula I, wherein

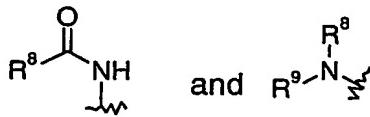
25 R^1 is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl,
cyclopropylmethyl, cyclohexylethyl, cyclopentylethyl, tetrahydropyranylmethyl,
tetrahydrofuranyl methyl, 1-piperidinylethyl, N-methyl-2-piperidinylmethyl and
benzyl;

R^2 is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-methoxy-2-
30 propyl, 2-hydroxyl-propyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-
buten-1-yl, ethyl, and 2-propyl;

Ar is selected from phenyl, pyridyl, pyrimidyl, thiazolyl, thiaryl, isoxazolyl, imidazolyl, and pyrazolyl;

n is selected from 0, 1 and 2;

each of R³ is independently selected from -H, C₁₋₃alkyl, 4-morpholinyl, 1-



5 piperidinyl, 1-piperazinyl, ; and

wherein 4-morpholinyl, 1-piperidinyl, and 1-piperazinyl are optionally substituted with one or more methyl; and wherein

each of R⁸ and R⁹ is independently selected from -H, C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl, wherein said

10 C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl are optionally substituted by one or more groups selected from hydroxy, amino and dimethylamino.

It will be understood that when compounds of the present invention contain

15 one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I.

Within the scope of the invention are also salts of the compounds of the formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiavascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

5 Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental 10 illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse 15 and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation).

20 Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

25 A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, or pharmaceutically 30 acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to 5 administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for 10 the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, 15 intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the 20 disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. 25 Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

30 In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

5 Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the
10 active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For
15 example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the
20 active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical
25 formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

30 A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I for the manufacture of a medicament for the therapy of pain.

5 Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

10 A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such therapy.

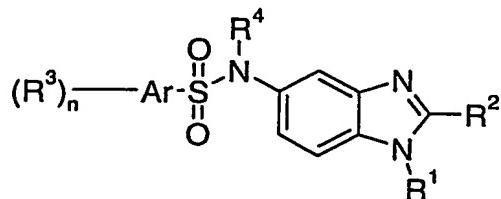
15 Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

20 Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

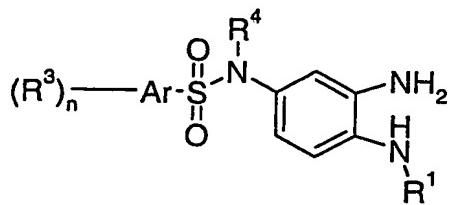
25 In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of formula I,



I

30 comprising the step of reacting a compound of formula II,

II

with a compound of R^2COX , in the presence of a base, such as an alkylamine, and optionally a coupling reagent, such as HATU, EDC, followed by treatment with an

5 acid, such as HCl, acetic acid

wherein

X is selected from Cl, Br, F and OH;

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl,
 R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-$

10 C_{1-6} alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl-
 C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl-
 C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl,

C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$,
 $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$, C_{6-10} aryl, C_{6-10} aryl-

15 $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl-
 $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl,
 C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl,
 C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino,
 C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl or

20 C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more
groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy,
and $-NR^5R^6$;

R^2 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl,

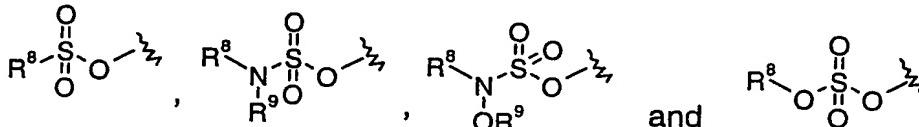
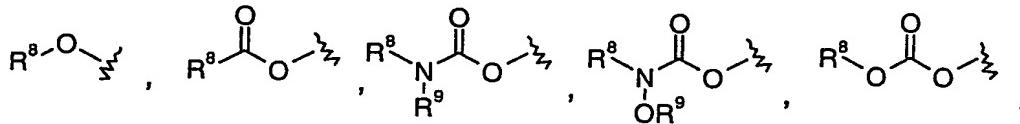
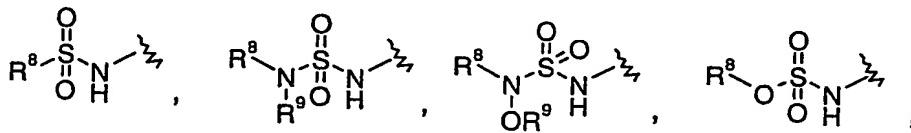
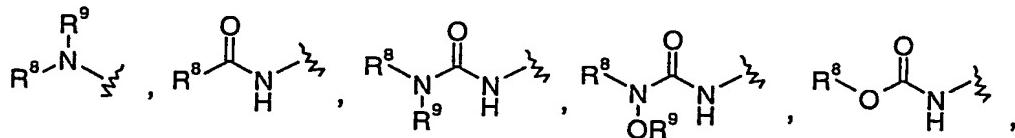
25 R^5R^6N- , C_{3-5} sheteroaryl, C_{6-10} aryl and C_{3-6} heterocycloalkyl, wherein
said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl,
 C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, C_{3-6} sheteroaryl, C_{6-10} aryl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally
substituted by one or more groups selected from halogen, cyano, nitro, methoxy,
30 ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$.

wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵, R⁶ or R⁷ forms a portion of a ring;

Ar is selected from C₆₋₁₀aryl and C₃₋₅heteroaryl;

5 n is selected from 0, 1, 2 and 3;

each of R³ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl optionally substituted with one or more groups selected from C₁₋₆alkyl, halogen, amino and C₁₋₆alkoxy,



10

and

;

each of R⁸ and R⁹ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, and a divalent C₁₋₆group that together with another divalent group selected from R⁸ and R⁹ forms a portion of a ring,

15 wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, or divalent C₁₋₆group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶; and

R⁴ is selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl,

20 C₃₋₁₀cycloalkyl-C₁₋₆alkyl, and C₄₋₈cycloalkenyl-C₁₋₆alkyl.

Particularly, the present invention provides a method of preparing a compound of formula I,

X is selected from Cl, Br, F and OH;

R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, phenyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl-

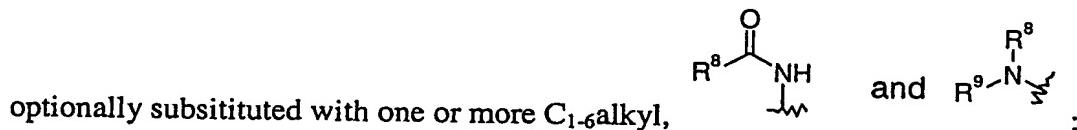
- 5 C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₄₋₆cycloalkenyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, phenyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₄₋₆cycloalkenyl used in defining R¹ is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

10 R² is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkyl-C₁₋₄alkyl used in defining R² is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

- 15 Ar is selected from phenyl and C₃₋₅sheteroaryl and

n is selected from 0, 1 and 2;

each of R³ is independently selected from -H, C₁₋₃alkyl, C₃₋₆heterocycloalkyl



wherein said C₃₋₆heterocycloalkyl contain at least one nitrogen ring atom and

- 20 the radical of C₃₋₆heterocycloalkyl is located on the at least one nitrogen ring atom, and wherein ;

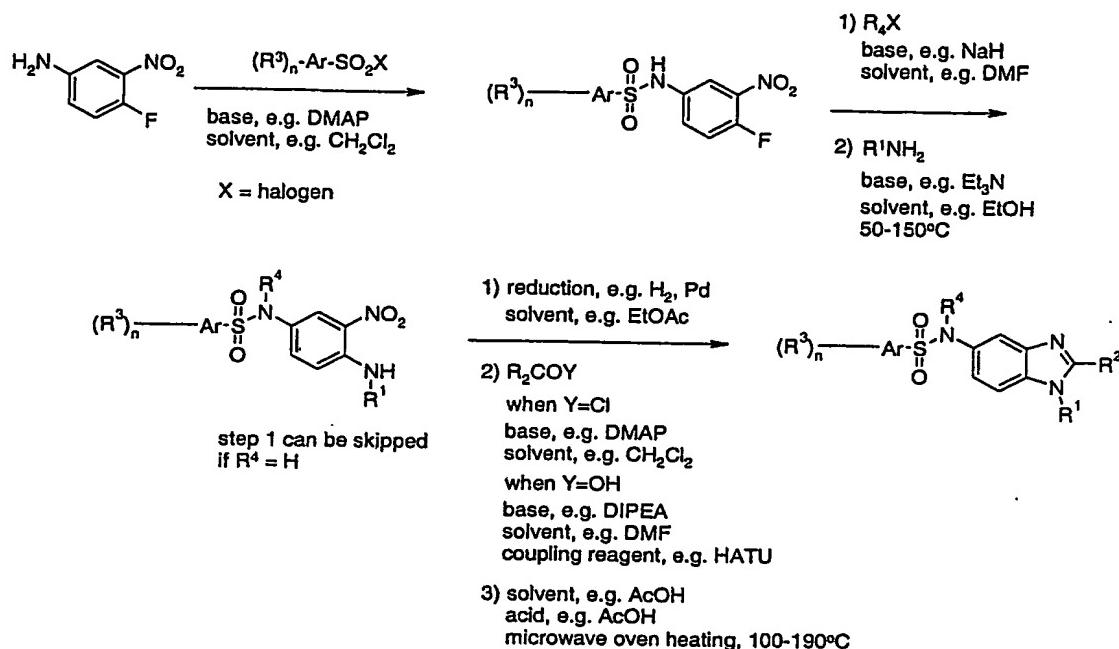
each of R⁸ and R⁹ is independently selected from -H, C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl, wherein said C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶; and

R⁴, R⁵ and R⁶ are independently selected from -H and C₁₋₃alkyl.

Compounds of the present invention may also be prepared according to the

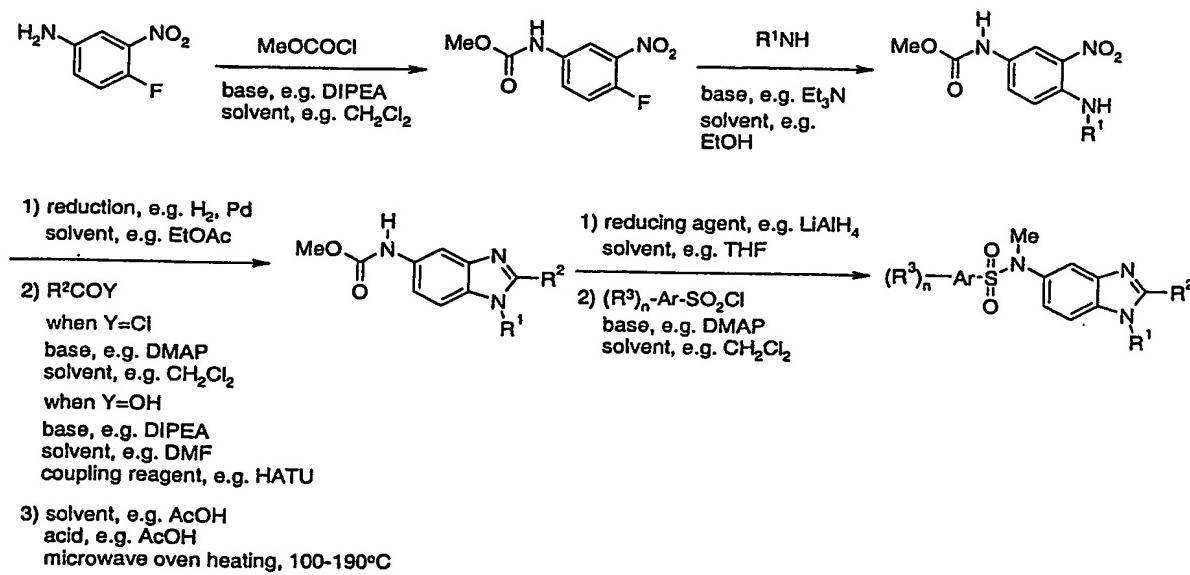
- 30 synthetic routes as depicted in Schemes 1-7.

Scheme 1. A synthetic route used for the synthesis of compounds including Examples 1-3 and 7-13.

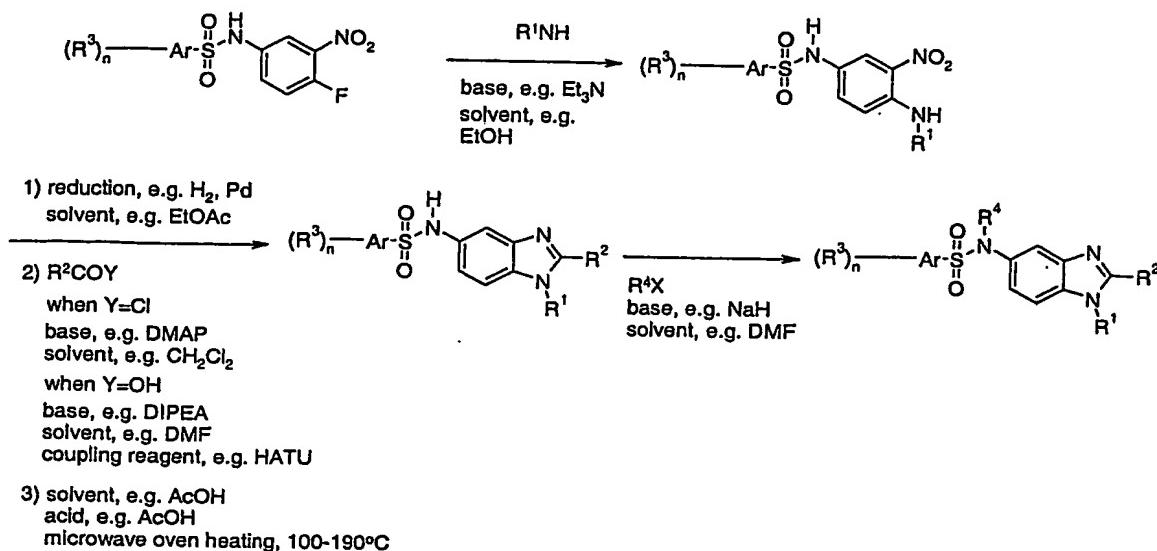


n, Ar, R¹, R², R³ and R⁴ are as defined in the specifications.

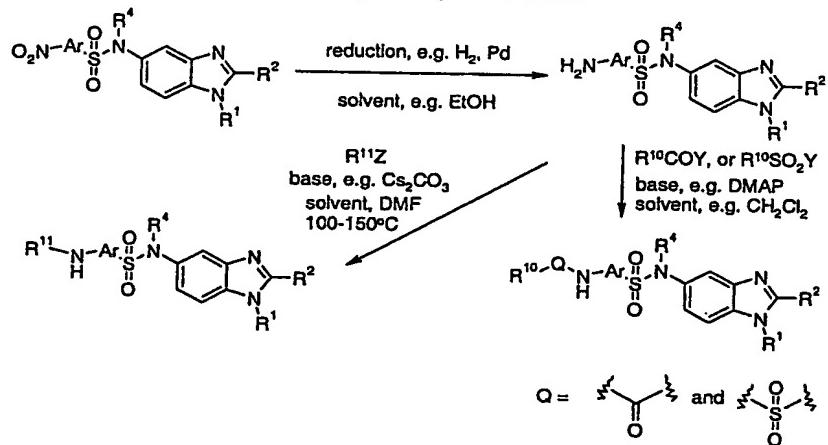
Scheme 2. A synthetic route used for the synthesis of compounds including Examples 4 to 6 and 24-26



n, Ar, R¹, R² and R³ are as defined in the specifications.

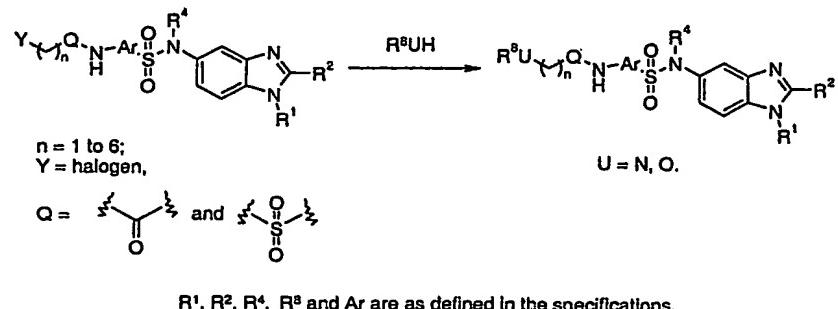
Scheme 3. A synthetic route used for the synthesis of compounds including Examples 14 to 23

n , Ar, R^1 , R^2 , R^3 and R^4 are as defined in the specifications.

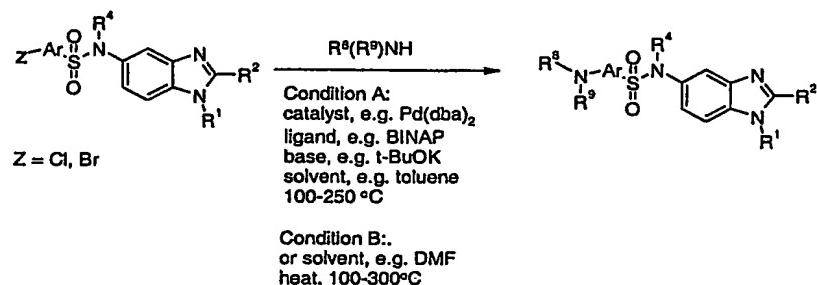
Scheme 4. A synthetic route used for the synthesis of compounds including Examples 27 to 32.

R^1 , R^2 , R^4 and Ar are as defined in the specifications;
 R^{10} and R^{11} are optionally substituted C1-6alkyl;
Y and Z are halogen or $-OH$.

Scheme 5. A synthetic route used for the synthesis of compounds including Examples 33 to 38.

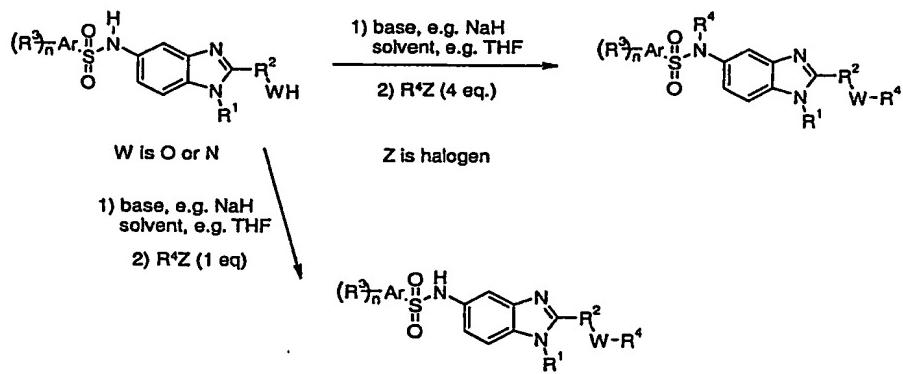


Scheme 6. A synthetic route used for the synthesis of compounds including Examples 39 and 40.



R¹, R², R⁴, R⁸, R⁹ and Ar are as defined in the specifications.

Scheme 7. A synthetic route used for the synthesis of compounds including Examples 44 and 45.



Biological Evaluation

hCB₁ and hCB₂ receptor binding

Human CB₁ receptor from Receptor Biology (hCB1) or human CB₂ receptor from BioSignal (hCB2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC₅₀ of the compounds of the invention at hCB₁ and hCB₂ are evaluated from 10-point dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 μl. The total and non-specific binding are determined in the absence and presence of 0.2 μM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μl/well of MS-20 scintillation liquid.

15

hCB₁ and hCB₂ GTPγS binding

Human CB₁ receptor from Receptor Biology (hCB1) or human CB₂ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 0.1% BSA). The EC₅₀ and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300μl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPg³⁵S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 μM (hCB₂) or 10 μM (hCB₁) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 μM (hCB2) or 112.5 μM (hCB₁) GDP prior to distribution in plates (15 μM (hCB₂) or 30 μM (hCB₁) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM MgCl₂, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant

concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the
5 following equation:

$$Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that
10 moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

Using the above-mentioned assays, the Ki towards human CB₁ receptors for most compounds of the invention is measured to be in the range of 0.7-5900 nM. The
15 Ki towards human CB₂ receptors for most compounds of the invention is measured to be in the range of about 0.3-5800 nM. The EC₅₀ towards human CB₁ receptors for most compounds of the invention is measured to be in the range of about 0.8-2800 nM. The E_{max} towards human CB₁ receptors for most compounds of the invention is measured to be in the range of about 22.3-125%.

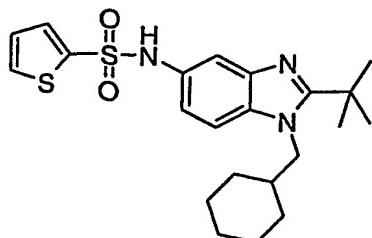
20 In a particular embodiment, the Ki towards human CB₁ receptors for most compounds of the invention is measured to be in the range of 0.7-50 nM. The Ki towards human CB₂ receptors for most compounds of the invention is measured to be in the range of about 0.3-25 nM. The EC₅₀ towards human CB₁ receptors for most compounds of the invention is measured to be in the range of about 0.8-100 nM. The
25 E_{max} towards human CB₁ receptors for most compounds of the invention is measured to be in the range of about 60-125%.

EXAMPLES

30 The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

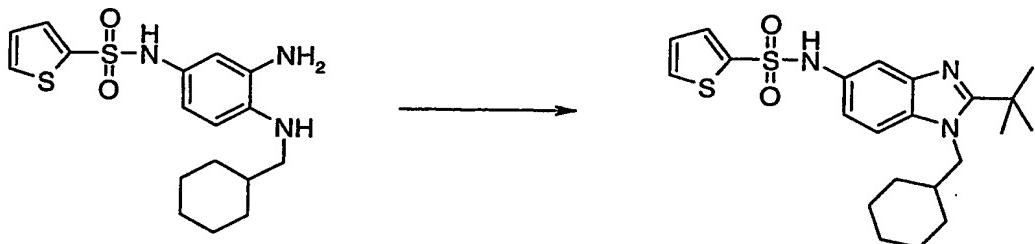
Example 1

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide



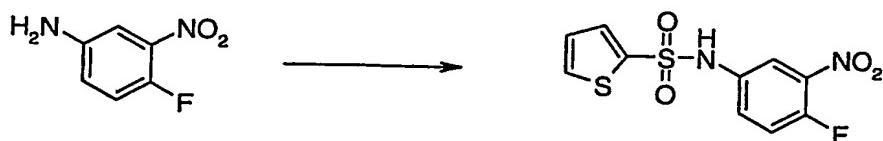
5

Step A. N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide



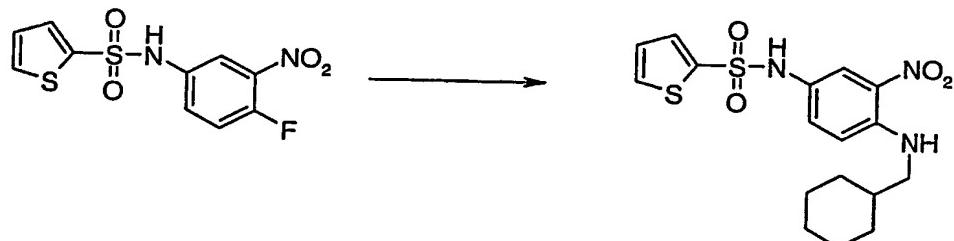
N-[3-Amino-4-[(cyclohexylmethyl)amino]phenyl]thiophene-2-sulfonamide (55 mg,

- 10 0.150 mmol) (for preparation, see the following steps B, C and D) was dissolved in 3 mL of 1,2-dichloroethane containing TEA (0.030 mL, 0.225 mmol). Trimethylacetyl chloride (0.020 mL, 0.165 mmol) was added dropwise and the solution was stirred at rt for 1h. Glacial AcOH (1 mL) and a few drops of concentrated HCl were added and the solution was stirred at 80°C overnight. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 2M NaOH aqueous solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 10 mg (15%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.19 (m, 5 H), 1.57 (m, 1 H), 1.59 (m, 1 H), 1.61 (s, 9 H), 1.66 (m, 1 H), 1.73 (m, 2 H), 2.05 (m, 1 H), 4.37 (d, J=7.62 Hz, 2 H), 7.02 (dd, J=4.98, 3.81 Hz, 1 H), 7.25 (dd, J=8.98, 2.15 Hz, 1 H), 7.52 (dd, J=3.71, 1.37 Hz, 1 H), 7.66 (d, J=2.15 Hz, 1 H), 7.69 (dd, J=5.08, 1.37 Hz, 1 H), 7.76 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 432.1; Anal. Calcd for C₂₂H₂₉N₃O₂S₂ + 1.4 TFA + 0.6 H₂O: C, 49.48; H, 5.29; N, 6.98. Found: C, 49.47; H, 5.36; N, 6.83.

Step B. N-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide

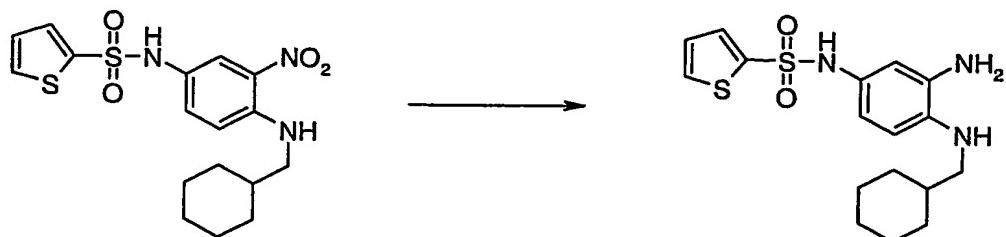
4-Fluoro-3-nitroaniline (1.00 g; 6.41 mmol) and 2-thiophenesulfonyl chloride (1.75 g, 9.62 mmol) were stirred in dichloromethane (150 mL) containing DMAP (1.17 g, 9.62 mmol) at rt for 24 h. The solution was washed with 5% KHSO₄ aqueous solution, saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 425 mg (22%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 6.90 (m, 1H), 7.08 (dd, J = 5.08, 3.91 Hz, 1H), 7.26 (t, J = 10.35 Hz, 1H), 7.49 (m, 1H), 7.56 (dd, J = 3.71, 1.37 Hz, 1H), 7.63 (dd, J = 5.08, 1.37 Hz, 1H), 7.78 (dd, J = 6.35, 2.83 Hz, 1H).

Step C. N-[4-[(Cyclohexylmethyl)amino]-3-nitrophenyl]thiophene-2-sulfonamide



N-(4-Fluoro-3-nitrophenyl)thiophene-2-sulfonamide (73 mg, 0.241 mmol) and cyclohexylmethyl amine (0.040 mL, 0.289 mmol) were stirred in 3 mL of EtOH containing TEA (0.050 mL, 0.361 mmol) at 75°C for 6h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica gel. Yield: 60 mg (63%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.03 (m, 2H), 1.26 (m, 3H), 1.61 (m, 2H), 1.76 (m, 2H), 1.82 (m, 4H), 3.13 (dd, J = 6.64, 5.47 Hz, 2H), 6.46 (m, 1H), 6.82 (d, J = 9.18 Hz, 1H), 7.05 (dd, J = 4.98, 3.81 Hz, 1H), 7.40 (dd, J = 9.18, 2.54 Hz, 1H), 7.47 (dd, J = 3.71, 1.37 Hz, 1H), 7.59 (dd, J = 5.08, 1.37 Hz, 1H), 7.73 (d, J = 2.73 Hz, 1H), 8.17 (m, 1H).

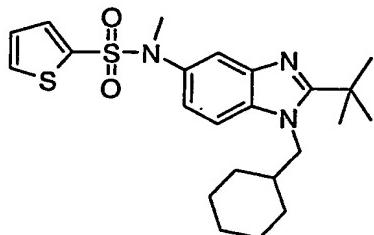
Step D. *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)thiophene-2-sulfonamide



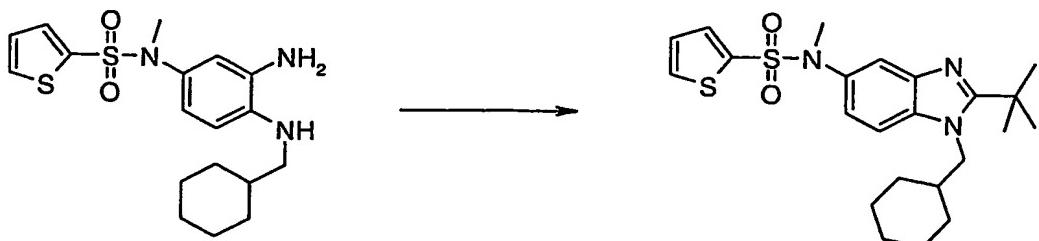
- 5 *N*-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)thiophene-2-sulfonamide (60 mg, 0.152 mmol) was dissolved in 5 mL of DMF under nitrogen. Tin (II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt for 6h. More tin(II) chloride dihydrate (170 mg, 0.760 mmol) was added and the solution stirred at rt overnight. The reaction mixture was quenched by addition of saturated NaHCO₃ solution at 0°C. The solution was then extracted (2X) with EtOAc and washed with brine and dried over anhydrous MgSO₄. The product was used directly for Step A without further purification. Yield: 55 mg (99%); MS (ESI) (M+H)⁺ 366.14.
- 10

Example 2

- 15 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide



Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide

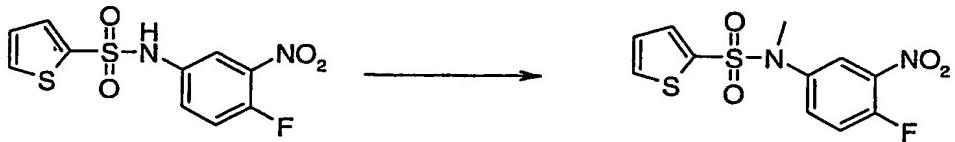


Following the procedure for Step A in Example 1, using *N*-(3-amino-4-[(cyclohexylmethyl) amino]phenyl)-*N*-methylthiophene-2-sulfonamide (115 mg, 0.303 mmol) (for preparation, see the following steps B, C and D) and trimethylacetyl chloride (0.041 mL, 0.333 mmol) in 3mL of DCE. The product was purified by

5 reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 65 mg (38%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.22 (m, 5 H), 1.61 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 2.08 (m, 1 H), 3.29 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.15 (dd, J=5.08, 3.71 Hz, 1 H), 7.33 (dd, J=8.98, 1.95 Hz, 1 H), 7.40 (dd, J=3.71, 1.37 Hz, 1 H), 7.55 (d, J=1.56 Hz, 1 H), 7.81 (dd, J=5.08, 1.37 Hz, 1 H), 7.85 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 446.1; Anal. Calcd for C₂₃H₃₁N₃O₂S₂ + 1.5 TFA + 0.1 H₂O: C, 50.49; H, 5.33; N, 6.79. Found: C, 50.55; H, 5.39; N, 6.76.

10

Step B. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide



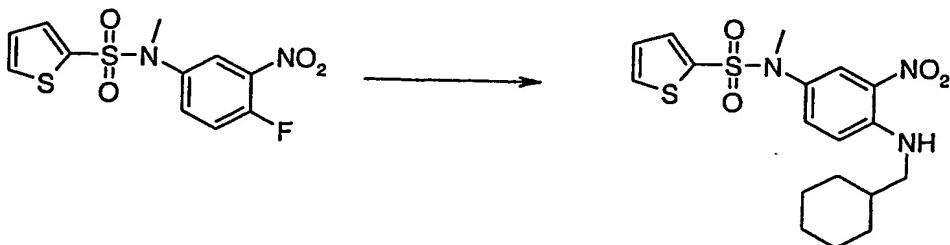
15 A solution of *N*-(4-fluoro-3-nitrophenyl)thiophene-2-sulfonamide (100 mg, 0.331 mmol) in MDF (1 mL) was added to a cold (0°C) stirring DMF solution (2 mL) of NaH (60% dispersion in oil) (20 mg, 0.496 mmol) under nitrogen. The solution was stirred at 0°C for 20 min. Methyl iodide (0.060 mL, 0.993 mmol) was added

20 dropwise and the solution stirred at rt for 3h. The reaction mixture was quenched at 0°C by the slow addition of saturated NH₄Cl solution. The solvent was evaporated *in vacuo*. The crude product was dissolved in EtOAc and washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The product was purified by flash chromatography with dichloromethane as eluent on silica gel to afford the title product. Yield: 78 mg (74%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.22 (s, 3H), 7.10 (dd, J = 4.98, 3.81Hz, 1H), 7.26 (dd, J= 3.91, 1.37Hz, 1H), 7.56 (m, 1H), 7.63 (dd, J = 5.08, 1.37Hz, 1H), 7.69 (dd, J = 6.44, 2.73Hz, 1H).

25

Step C. *N*-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide

30

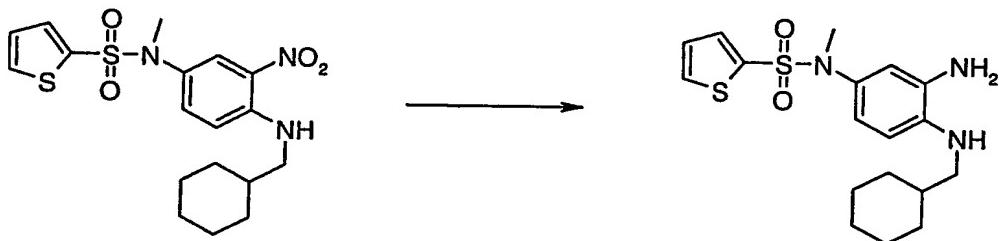


Following the procedure for Step C in Example 1, using *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide (3) (100 mg, 0.316 mmol),

methylcyclohexylamine (0.050 mL, 0.379 mmol) and TEA (0.050mL, 0.474mmol) in

- 5 3mL of EtOH. The product was used directly for the next step without any column chromatography purification. Yield: 130 mg (99%); ¹H NMR (400 MHz,
CHLOROFORM-D) δ 0.98 (m, 1H), 1.04 (m, 1H), 1.20 (m, 1H), 1.66 (m, 2H), 1.75
(m, 2H), 1.81 (d, J = 12.50Hz, 2H), 3.12 (m, 2H), 3.16 (s, 3H), 6.80 (d, J = 9.37Hz,
1H), 7.09 (dd, J = 4.98, 3.81Hz, 1H), 7.37 (dd, J = 3.81, 1.27Hz, 1H), 7.42 (dd, J =
10 9.28, 2.64Hz, 1H), 7.59 (dd, J = 4.98, 1.27Hz, 1H), 7.65 (d, J = 2.54Hz, 1H), 8.20 (m,
1H).

Step D. *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)-*N*-methylthiophene-2-sulfonamide

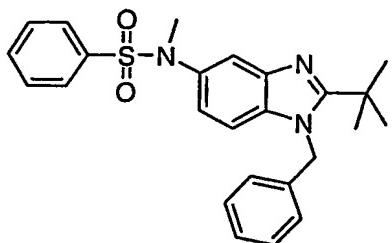


15

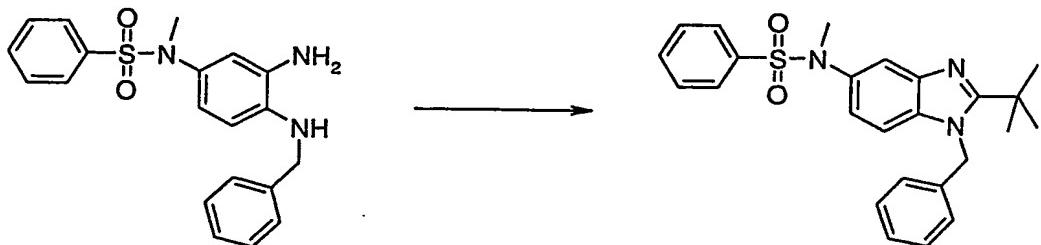
Following the procedure for Step D in Example 1, using *N*-(4-[(cyclohexylmethyl)amino]-3-nitrophenyl)-*N*-methylthiophene-2-sulfonamide (125 mg, 0.305 mmol) and tin(II) chloride dihydrate (2X345 mg, 2X1.52 mmol). The product was used directly for Step A without further purification. Yield: 115 mg
20 (99%); MS (ESI) (M+H)⁺ 379.97.

Example 3

N-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide



Step A. *N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzenesulfonamide



- 5 Following the procedure for Step A in Example 1, using *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)-*N*-methylbenzenesulfonamide (88mg, 0.239mmol), trimethylacetyl chloride (0.032mL, 0.262mmol) and DMAP (7.0mg, 0.060mmol) in 5 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 38 mg (29%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.62 (s, 9 H), 3.21 (s, 3 H), 5.93 (s, 2 H), 7.09 (m, 2 H), 7.12 (dd, J=8.98, 2.15 Hz, 1 H), 7.32 (m, 4 H), 7.48 (m, 4 H), 7.57 (dd, J=1.95, 0.59 Hz, 1 H), 7.62 (m, 1 H); MS (ESI) (M+H)⁺ 434.1; Anal. Calcd for C₂₅H₂₇N₃O₂S + 1.4 TFA + 0.2 H₂O: C, 55.95; H, 4.86; N, 7.04. Found: C, 55.90; H, 4.85; N, 7.06.
- 10
- 15

Step B. *N*-(4-Fluoro-3-nitrophenyl)benzenesulfonamide



- 20 4-Fluoro-3-nitroaniline (2.00 g, 12.8 mmol) was dissolved in 50 mL of pyridine containing a catalytic amount of DMAP. Benzenesulfonyl chloride (1.96 mL, 15.36 mmol) was added and the solution was stirred at rt for 3h. The solvent was evaporated. The crude product was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by flash chromatography using 2:1 / hexanes:EtOAc on silica

gel. Yield: 3.40 g (90%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 7.09 (m, 1H), 7.18 (dd, J = 9.96, 8.98 Hz, 1H), 7.40 (m, 1H), 7.48 (m, 2H), 7.58 (m, 1H), 7.71 (dd, J = 6.25, 2.73 Hz, 1H), 7.76 (m, 2H).

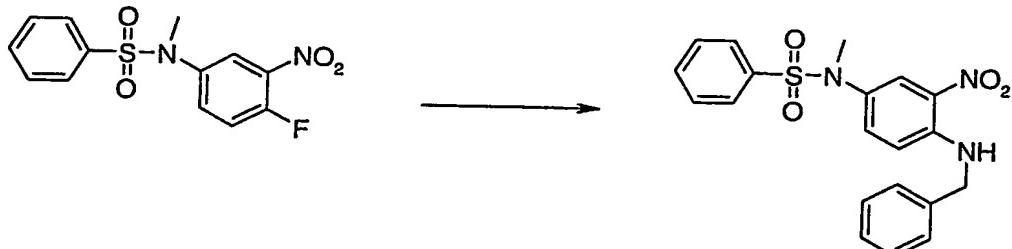
5 **Step C. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide**



Following the procedure for Step B in Example 2, using *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (1.00 g, 3.38 mmol), NaH (60% dispersion in oil) (160 mg, 4.06 mmol) and methyl iodide (0.315 mL, 5.07 mmol) in 25 mL of DMF.

- 10 The product was purified by flash chromatography using dichloromethane as eluent on silica gel. Yield: 815 mg (78%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 3.19 (s, 3H), 7.28 (m, 1H), 7.51 (m, 1H), 7.54 (m, 2H), 7.57 (m, 1H), 7.65 (m, 2H).

Step D. *N*-[4-(Benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide



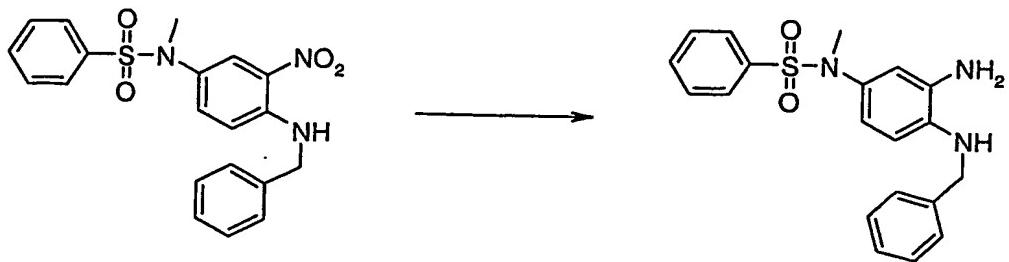
15

Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (71 mg, 0.229 mmol), benzylamine (0.030 mL, 0.275 mmol) and TEA (0.050 mL, 0.344 mmol) in 3 mL of EtOH. The product was used directly for the next step without further purification. Yield: 99 mg (99%); ^1H NMR

- 20 (400 MHz, CHLOROFORM-D) δ 3.12 (s, 3H), 4.56 (d, J = 5.47 Hz, 2H), 6.81 (d, J = 9.18 Hz, 1H), 7.34 (m, 3H), 7.40 (m, 3H), 7.49 (m, 2H), 7.57 (m, 1H), 7.60 (m, 1H), 7.64 (dd, J = 4.30, 1.95 Hz, 1H), 8.47 (m, 1H).

Step E. *N*-(3-Amino-4-[(cyclohexylmethyl)amino]phenyl)-*N*-methylbenzenesulfonamide

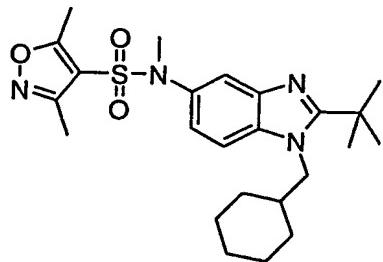
25



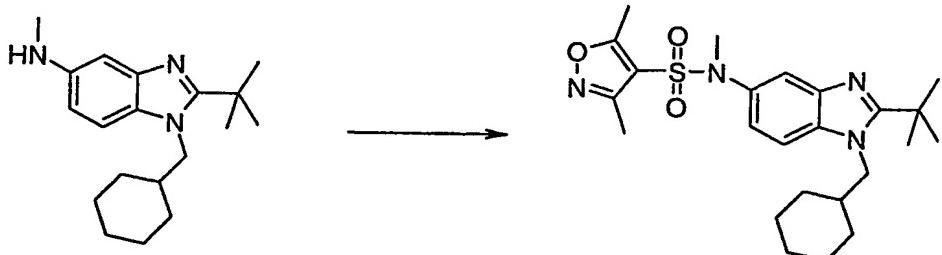
N-[4-(Benzylamino)-3-nitrophenyl]-*N*-methylbenzenesulfonamide (95 mg, 0.239 mmol) was dissolved in 15 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt for 4h. The solution was filtered through Celite and the solvent was evaporated. The product was used directly for Step A without further purification. Yield: 88 mg (99%); MS (ESI) (M+H)⁺ 367.97.

Example 4

- 10 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethyloxazole-4-sulfonamide



Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethyloxazole-4-sulfonamide

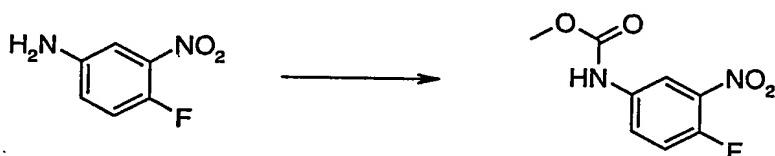


15

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (35 mg, 0.117 mmol) (for preparation, see the following steps B, C, D, E and F) and 3,5-dimethyloxazole-4-sulfonyl chloride (0.030 mg, 0.140 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The

solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (73%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.58 (m, 2 H), 1.65 (s, 10 H), 1.74 (m, 2 H), 1.88 (s, 3 H), 2.08 (m, 1 H), 2.33 (s, 3 H), 3.31 (s, 3 H), 4.46 (d, J=7.81 Hz, 2 H), 7.47 (dd, J=8.98, 1.95 Hz, 1 H), 7.68 (d, J=1.76 Hz, 1 H), 7.91 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 459.2; Anal. Calcd for C₂₄H₃₄N₄O₃S + 1.6 TFA + 0.2 H₂O: C, 50.68; H, 5.63; N, 8.69. Found: C, 50.70; H, 5.65; N, 8.81.

10 Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate

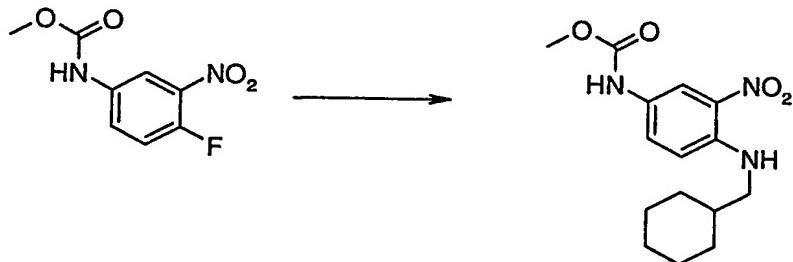


Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight.

15 The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3 H), 7.02 (s, 1 H), 7.23 (m, 1 H), 7.72 (d, J=8.59 Hz, 1 H), 8.17 (dd, J=6.35, 2.64 Hz, 1 H).

20

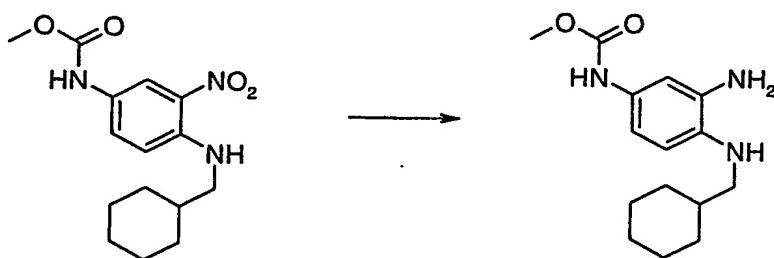
Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃

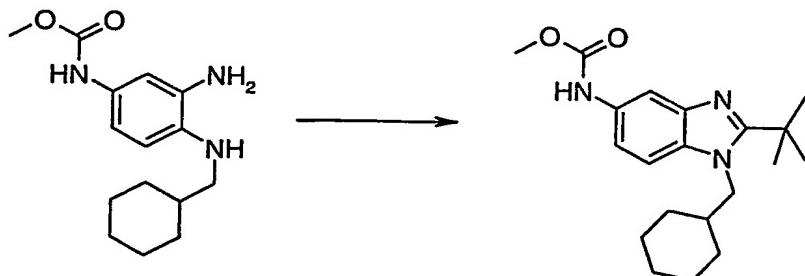
solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.04 (ddd, J = 24.02, 12.11, 2.93 Hz, 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 5 3.14 (dd, J = 6.44, 5.66 Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, J = 9.37 Hz, 1H), 7.63 (m, 1H), 8.05 (d, J = 2.54 Hz, 1H), 8.09 (m, 1H).

Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate



- 10 Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent was evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%). MS (ESI) (M+H)⁺ 277.9.
- 15

Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate

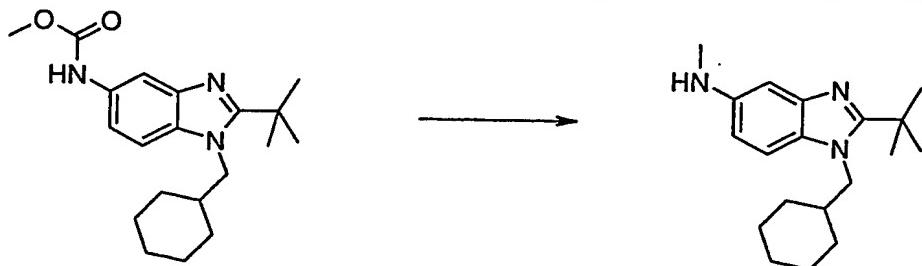


- 20 Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The

residue was divided in two portions and each of them was dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The contents of the two tubes were combined and the solvent was

5 evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%);
¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H),
1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s,
10 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H),
7.59 (d, J = 1.76 Hz, 1H).

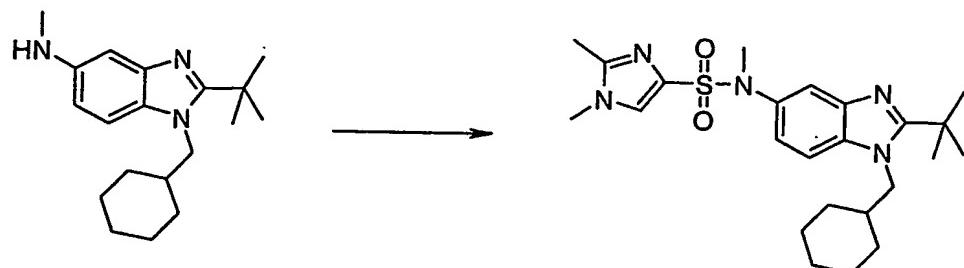
Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-N-methyl-1*H*-benzimidazol-5-amine



- 15 Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution was stirred at 0°C for 15min. LiAlH₄ (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of
20 MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 (s, 2 H) 1.17 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 2 H) 1.67 (m, 2 H) 1.72 (m, 2 H) 2.02 (m, 1 H) 2.87 (s, 3 H) 4.06 (d, J=7.62 Hz, 2 H) 6.60 (dd, J=8.69, 2.25 Hz, 1 H) 7.00 (d, J=1.76 Hz, 1 H) 7.12 (d, J=8.59 Hz, 1 H).
- 25

Example 5

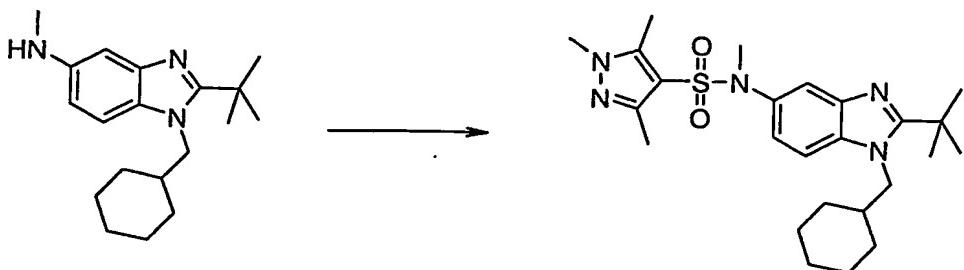
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-4-sulfonamide



- 5 Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,2-dimethyl-1*H*-imidazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP (catalytic) in 3 mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound
- 10 as the corresponding TFA salt. Yield: 47 mg (69%); ¹H NMR (400 MHz, METHANOL-D₄) δ1.22 (m, 5 H), 1.62 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.09 (m, 1 H), 2.34 (s, 3 H), 3.28 (s, 3 H), 3.61 (s, 3 H), 4.43 (d, J=7.62 Hz, 2 H), 7.43 (dd, J=8.98, 2.15 Hz, 1 H), 7.51 (s, 1 H), 7.66 (d, J=1.95 Hz, 1 H), 7.82 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 458.2; Anal. Calcd for C₂₄H₃₅N₅O₂S + 1.7 TFA + 0.1 H₂O: C, 50.38; H, 5.69; N, 10.72. Found: C, 50.39; H, 5.73; N, 10.73.
- 15

Example 6

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,3,5-tetramethyl-1*H*-pyrazole-4-sulfonamide

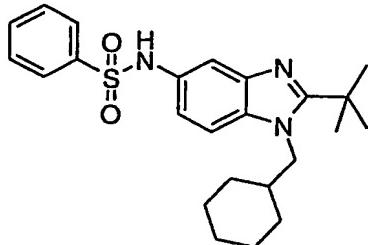
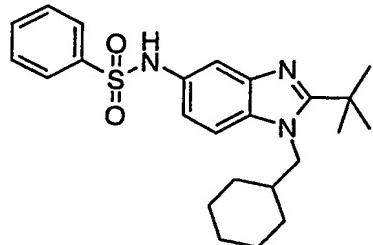


20

Following the procedure for Step A in Example 4, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (19) (36 mg, 0.120 mmol), 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonyl chloride (30 mg, 0.144 mmol) and DMAP

(catalytic) in 3mL of dichloromethane. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 49 mg (70%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.20 (m, 5 H), 1.56 (m, 2 H), 1.65 (s, 9 H), 1.67 (m, 1 H), 1.74 (m, 2 H), 1.80 (s, 3 H), 2.08 (m, 1 H), 2.16 (s, 3 H), 3.21 (s, 3 H), 3.69 (s, 3 H), 4.44 (d, J=7.81 Hz, 2 H), 7.38 (dd, J=9.08, 2.05 Hz, 1 H), 7.62 (d, J=1.56 Hz, 1 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 472.2; Anal. Calcd for C₂₅H₃₇N₅O₂S + 1.2 TFA + 0.4 H₂O: C, 53.45; H, 6.38; N, 11.37. Found: C, 53.50; H, 6.38; N, 11.29.

10 Example 7

*N-[2-tert-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide*Step A. *N-[2-tert-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulfonamide*

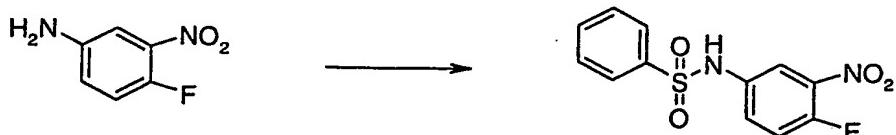
15

DMAP (44.0 mg, 0.36 mmol) and then trimethylacetyl chloride (199.0 mg, 1.65 mmol) at 0 °C was added into a solution of *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)benzene sulfonamide (540.1 mg, 1.5 mmol) (for preparation, see the following steps B, C and D) in dichloromethane (40 mL). The mixture was stirred for 5 h at room temperature. After evaporation of the solvent, the residue was dissolved in 1,2-dichloroethane (5x5 mL) in five Teflon-capped test tubes. The vessels were irradiated by microwave for 2h at 170 °C. The combined reaction mixture diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (10 mL) and dried over Na₂SO₄. After filtration and evaporation, the residue

was purified by MPLC (hex/EtOAc 1:1 on silica gel) to give 568.2 mg (89%) of a white solid as the title compound. Part of the product was converted to TFA salt.

¹HNMR (400 MHz, CD₃OD): δ 1.18 (m, 5 H), 1.55 (m, 2 H), 1.59 (s, 9 H), 1.65 (m, 1 H), 1.71 (m, 2 H), 2.03 (m, 1 H), 4.34 (d, J=7.42 Hz, 2 H), 7.20 (d, J=9.18 Hz, 1 H), 7.44 (m, 2 H), 7.53 (m, 1 H), 7.58 (s, 1 H), 7.70 (d, J=8.79 Hz, 1 H), 7.76 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)⁺ = 426.1. Anal. Calcd for C₂₄H₃₁N₃O₂S+1.10 TFA+0.10 H₂O: C, 56.92; H, 5.89; N, 7.60. Found: C, 56.95; H, 5.92; N, 7.56.

Step B. *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide

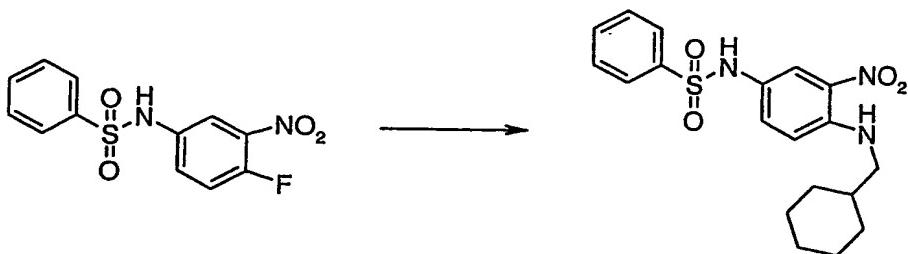


10

Benzenesulfonyl chloride (5.61 mL, 7.74 g, 44 mmol) was added into a solution of 4-fluoro-3-nitro-aniline (6.24 g, 40 mmol) in pyridine (40 mL) at 0 °C. The reaction mixture was stirred for two days at room temperature. Upon evaporation of the solvent, the residue was dissolved in EtOAc (500 mL), washed with water (50 mL), 15 2N HCl (2x50 mL), water (50 mL), sat. sodium bicarbonate aqueous solution (2x50 mL), sat. sodium chloride aqueous solution (2x50 mL) and dried over sodium sulphate. After filtration and concentration, 12.1 g (100%) of a brown solid was obtained as the title compound. ¹HNMR (400 MHz, CD₃Cl): δ 7.20 (m, 2 H), 7.44 (m, 1 H), 7.52 (m, 2 H), 7.61 (m, 1 H), 7.75 (dd, J=6.25, 2.73 Hz, 1 H), 7.81 (m, 2 H).

20

Step C: *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}benzenesulfonamide

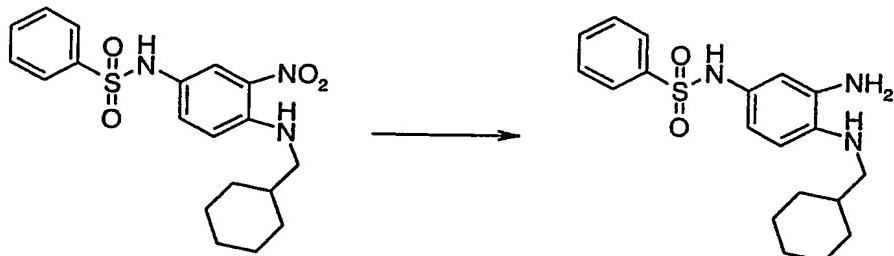


Cyclohexylmethylamine (3.48 mL, 3.03 g, 26.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)benzenesulfonamide (3.60 g, 12.1 mmol) in 60 mL of EtOH-

25 H₂O (1:1 V/V) at room temperature. The reaction mixture was heated for 48 h at 60 °C, and allowed to cool to room temperature and concentrated to a small volume, and

then extracted with EtOAc. The crude product was purified by MPLC using Hex/EtOAc (4:1) on silica gel to give 3.75 g (79%) of an orang-red solid as the title compound. ^1H NMR (400 MHz, CD₃Cl): δ 1.05 (m, 2 H), 1.24 (m, 3 H), 1.72 (m, 6 H), 3.12 (dd, $J=6.64, 5.47$ Hz, 2 H), 6.23 (s, 1 H), 6.79 (d, $J=9.18$ Hz, 1 H), 7.36 (dd, $J=9.08, 2.64$ Hz, 1 H), 7.48 (m, 2 H), 7.58 (m, 1 H), 7.63 (d, $J=2.54$ Hz, 1 H), 7.72 (m, 2 H), 8.14 (s, 1 H).

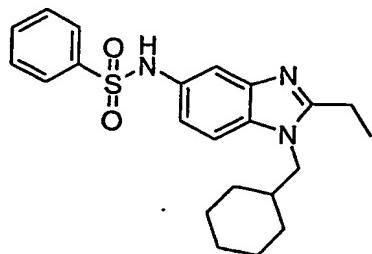
Step D: *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)benzenesulfonamide



- 10 *N*-(4-[(cyclohexylmethyl)amino]-3-nitrophenyl)benzenesulfonamide (3.75 g, 9.63 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.5 g) at 30-40 psi H₂ in Parr shaker for 20 h at room temperature. After filtration through Celite and concentration, 4.0 g (100%) of a light yellow solid was obtained as the title compound, which was used for Step A without further purification. ^1H NMR (400 MHz, CD₃Cl): δ 0.88 (m, 1 H), 0.99 (m, 2 H), 1.23 (m, 3 H), 1.56 (m, 1 H), 1.75 (m, 4 H), 2.86 (d, $J=6.64$ Hz, 2 H), 3.33 (s broad, 3 H), 6.30 (s broad, 1 H), 6.33 (dd, $J=8.30, 2.44$ Hz, 1 H), 6.41 (m, 1 H), 6.56 (d, $J=2.34$ Hz, 1 H), 7.41 (m, 2 H) 7.52 (m, 1 H), 7.70 (m, 2 H). MS (ESI) (M-H)⁺: 359.89.
- 15

20 **Example 8**

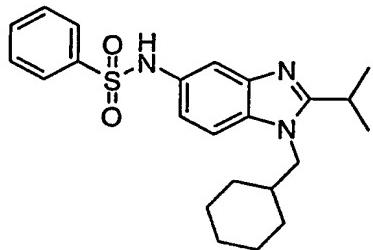
N-(1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl)benzenesulfonamide



Following the procedure for Step A in Example 7, using a solution *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)benzenesulfonamide (180.3 mg, 0.5 mmol) and

DMAP (15.0 mg, 0.12 mmol) in dichloromethane (15 mL), to which was added propionyl chloride (50.9 mg, 0.55 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature. The crude product was purified by MPLC (hex/EtOAc 1:9 on silica gel) to give 157.7 mg (79%) of a white solid as the title compound. Part of the
 5 product was converted to TFA salt. ^1H NMR (400 MHz, CD₃OD): δ 1.12 (m, 2 H), 1.21 (m, 3 H), 1.48 (t, J=7.62 Hz, 3 H), 1.60 (m, 2 H), 1.68 (m, 1 H), 1.73 (m, 2 H), 1.90 (m, 1 H), 3.18 (q, J=7.49 Hz, 2 H), 4.19 (d, J=7.62 Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.71 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H). MS (ESI) (M+H)⁺ = 398.1

10

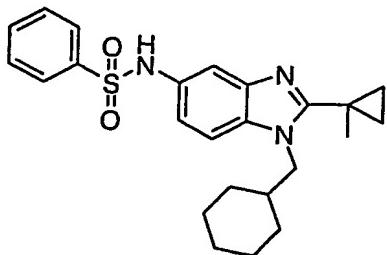
Example 9*N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzene sulfonamide

Following the procedure for Step A in Example 7, using *N*-(3-amino-4-

15 [(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (182.1 mg, 0.5 mmol), DMAP (15.0 mg, 0.12 mmol) and isobutyryl chloride (50.2 mg, 0.56 mmol) CH₂Cl₂ (15 mL). The crude product was purified by MPLC (Hex/EtOAc 1:1). Yield: 178.4 mg (86%). ^1H NMR (400 MHz, CD₃OD): δ 1.17 (m, 5 H), 1.47 (d, J=6.83 Hz, 6 H), 1.60 (m, 2 H), 1.72 (m, 3 H), 1.88 (m, 1 H), 3.62 (m, 1 H), 4.25 (d, J=7.62 Hz, 2 H),
 20 7.25 (dd, J=8.88, 2.05 Hz, 1 H), 7.48 (m, 2 H), 7.57 (m, 2 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)⁺ = 412.1.

Example 10*N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-

25 yl]benzenesulfonamide



Diisopropylethylamine (104.7 mg, 0.81 mmol) was added into a solution of *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl)benzene sulfonamide (195.6 mg, 0.543 mmol), and 1-methylcyclopropanecarboxylic acid (59.8 mg, 0.6 mmol) in DMF (5 mL) at 0 °C. Stirring for 20 min.

- HATU (246.4 mg, 0.65 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (10 mL) and heated for 20 h at 80 °C. Upon evaporation of the solvent, 93.7 mg of the acetate salt was lyophilized, and the rest was diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, 144.9 mg of the free amine as the title compound was obtained. Total yield: 99%. ¹HNMR (400 MHz, CD₃OD): δ 0.89 (m, 2 H), 1.10 (m, 4 H), 1.21 (m, 3 H), 1.45 (s, 3 H), 1.55 (d, 2 H), 1.69 (m, 3H), 2.08 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 7.01 (dd, J=8.79, 1.95 Hz, 1 H), 7.25 (d, J=1.95 Hz, 1 H), 7.35 (d, J=8.79 Hz, 1 H), 7.40 (t, J=7.62 Hz, 2 H), 7.50 (t, J=7.42 Hz, 1 H), 7.68 (d, J=7.42 Hz, 2 H). MS (ESI) (M+H)⁺ = 424.1. Anal. Calcd for C₂₄H₂₉N₃O₂S+0.4 AcOH+0.10 H₂O: C, 65.92; H, 6.98; N, 9.45. Found: C, 66.01; H, 6.89; N, 9.09.

20

Example 11

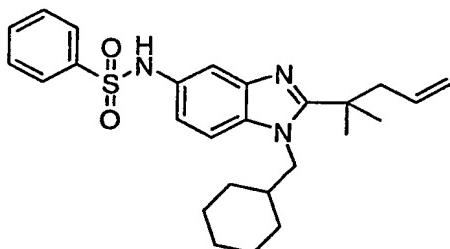
N-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



Following the procedure in Example 10, using *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-dimethylbutyric acid (63.9 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by reversed HPLC using 30-80% CH₃CN/H₂O to give 39.9 mg (14%) of a white solid as the title compound. ¹HNMR (400 MHz, CD₃OD): δ 0.81 (t, J=7.52 Hz, 3 H), 1.20 (m, 5 H), 1.58 (m, 2 H), 1.62 (s, 6 H), 1.68 (m, 1 H), 1.75 (m, 2 H), 1.97 (q, J=7.62 Hz, 2 H), 2.03 (m, 1 H), 4.37 (d, J=7.62 Hz, 2 H), 7.23 (dd, J=8.98, 1.95 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (m, 1 H), 7.73 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI) (M+H)⁺ = 440.2. Anal. Calcd for C₂₅H₃₃N₃O₂S+1.0 TFA+0.60 H₂O: C, 57.45; H, 6.29; N, 7.44. Found: C, 57.49; H, 6.39; N, 7.35.

Example 12

- 15 *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethyl-3-butenyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide

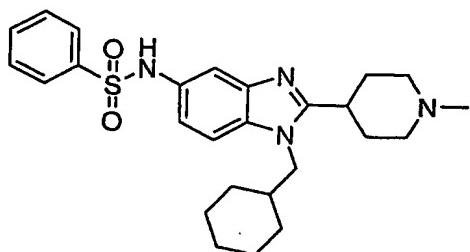


Following the procedure in Example 10, using *N*-(3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 2,2-dimethyl-4-pentenoic acid (70.5 mg, 0.55 mmol), diisopropylethylamine (96.6 mg, 0.75 mmol) and HATU (228.1 mg, 0.60 mmol)) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by by reversed HPLC using 30-80% CH₃CN/H₂O to give 38.2 mg (14%) of a white solid as the title compound. ¹HNMR (400MHz, CD₃OD): δ 1.19 (m, 5 H), 1.59 (m, 2 H), 1.65 (s, 6 H), 1.68 (m, 1 H,) 1.74 (m, 2 H), 2.04 (m, 1 H), 2.67 (d, J=7.42 Hz, 2 H), 4.40 (d, J=7.62 Hz, 2 H), 5.03 (s, 1 H), 5.07 (m, 1 H), 5.60 (m, 1 H), 7.23 (dd, J=8.98, 2.15 Hz, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.59 (d, J=1.56 Hz, 1 H), 7.74 (d, J=8.98 Hz, 1 H), 7.80 (m, 2 H). MS (ESI)

$(M+H)^+ = 452.2$. Anal. Calcd for $C_{26}H_{33}N_3O_2S + 1.2$ TFA: C, 57.97; H, 5.86; N, 7.14. Found: C, 58.00; H, 5.74; N, 7.06.

Example 13

- 5 *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide

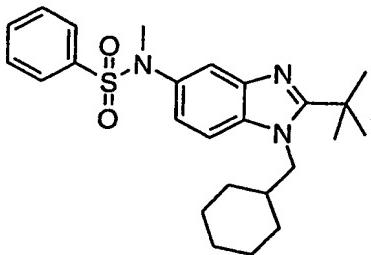


Following the procedure in Example 10: using *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (180.3 mg, 0.50 mmol), 1-

- 10 methylpiperidine 4-carboxylic acid hydrochloride (98.8 mg, 0.55 mmol), diisopropylethylamine (161.6 mg, 1.25 mmol) and HATU (228.1 mg, 0.60 mmol) in DMF (5 mL) and then in acetic acid (10 mL), the crude product was purified by MPLC using $CH_2Cl_2/MeOH$ (10:1) on silica gel to give 213.2 mg (91%) of a colorless syrup as the title compound. Part of the product was converted to TFA salt. 1H NMR (400 MHz, CD_3OD): δ 1.08 (m, 2 H), 1.18 (m, 3 H), 1.52 (m, 2 H), 1.68 (m, 3 H), 1.79 (m, 1 H), 2.15 (m, 4 H), 2.91 (s, 3 H), 3.18 (m, 2 H), 3.35 (m, 1 H), 3.62 (d, $J=13.28$ Hz, 2 H), 4.08 (d, $J=7.81$ Hz, 2 H), 7.04 (dd, $J=8.79, 1.95$ Hz, 1 H), 7.40 (m, 4 H), 7.50 (m, 1 H), 7.69 (m, 2 H). MS (ESI) $(M+H)^+ = 467.2$. Anal. Calcd for $C_{26}H_{34}N_4O_2S + 1.5$ TFA + 0.9 H_2O : C, 53.27; H, 5.75; N, 8.57. Found: C, 53.32; H, 5.569; N, 8.55.

Example 14

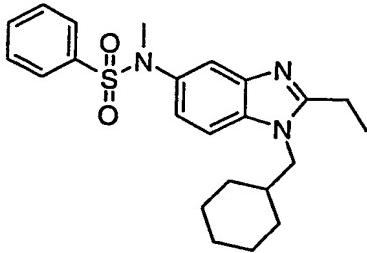
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



NaH (54.0 mg, 60%, 1.34 mmol) was added to a solution of *N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (258.5 mg, 0.607 mmol) in THF (15 mL) at 0 °C. After stirring for 1 h, MeI (259.8 mg, 1.83 mmol) was
 5 added. The mixture was stirred overnight at room temperature, quenched with sat. NaHCO₃ (5 mL). The two phases were separated. The aqueous was extracted with EtOAc (3x20 mL). The combined organic phases were washed with NaHCO₃ (2x10 mL) and dried with Na₂SO₄. After concentration, the residue was purified by MPLC using hex/EtOAc (1:1) on silica gel to give 216.5 mg (81%) of the title product, and
 10 converted to TFA salt as a white solid. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5 H), 1.60 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 1 H), 3.24 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.26 (dd, J=8.98, 2.15 Hz, 1 H), 7.50 (m, 5 H), 7.65 (m, 1 H), 7.81 (d, J=9.18 Hz, 1 H). MS (ESI) (M+H)⁺ = 440.2. Anal. Calcd for C₂₅H₃₃N₃O₂S+1.20 TFA: C, 57.09; H, 5.98; N, 7.29. Found: C, 57.07; H, 6.01; N,
 15 7.25.

Example 15

N-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide



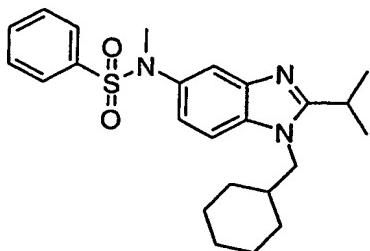
20 Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (91.3 mg, 0.23 mmol), sodium hydride (28.2 mg, 60%, 0.71 mmol) and iodomethane (97.9 mg, 0.69 mmol) in THF (10 mL). Yield: 69.7 mg (74%); white solid for TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5

H), 1.51 (t, $J=7.52$ Hz, 3 H), 1.65 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.95 (m, 1 H), 3.22 (q, $J=7.62$ Hz, 2 H), 3.27 (s, 3 H), 4.26 (d, $J=7.62$ Hz, 2 H), 7.29 (dd, $J=8.88$, 2.05 Hz, 1 H), 7.50 (d, $J=1.95$ Hz, 1 H), 7.54 (m, 4 H), 7.67 (m, 1 H), 7.80 (d, $J=8.98$ Hz, 1 H). MS (ESI) ($M+H$)⁺ = 412.1

5

Example 16

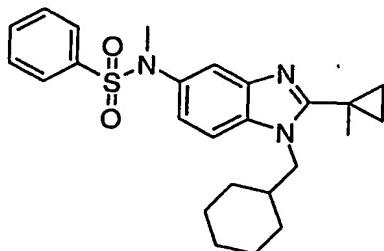
N-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide



- 10 Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzenesulfonamide (81.8 mg, 0.199 mmol), sodium hydride (24.0 mg, 60%, 0.596 mmol) and iodomethane (84.7 mg, 0.597 mmol) in THF (15 mL). Yield: 80.1 mg (95%); The title compound was converted to white solid as a TFA salt. ¹HNMR (400 MHz, CD₃OD): δ 1.20 (m, 5 H), 1.51 (d, $J=6.83$ Hz, 6 H), 1.64 (m, 2 H), 1.69 (m, 1 H), 1.76 (m, 2 H), 1.93 (m, 1 H), 3.27 (s, 3 H), 3.67 (m, 1 H), 4.31 (d, $J=7.62$ Hz, 2 H), 7.28 (m, 1 H), 7.54 (m, 5 H), 7.68 (m, 1 H), 7.81 (d, $J=8.98$ Hz, 1 H). MS (ESI) ($M+H$)⁺ = 426.1.
- 15

Example 17

- 20 *N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene sulfonamide

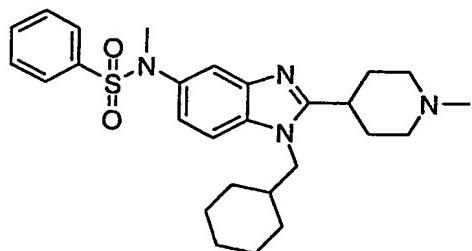


Following the procedure in Example 14, using *N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide (144.9 mg, 0.342

mmol), sodium hydride (30.0 mg, 60%, 0.752 mmol) and iodomethane (145.7 mg, 1.03 mmol) in THF (15 mL). Yield: 72.3 mg (48%); compound was converted to a white solid as a TFA salt. ^1H NMR (400 MHz, CD₃OD): δ 1.19 (m, 4 H), 1.26 (m, 3 H), 1.34 (m, 2 H), 1.59 (s, 3 H), 1.71 (m, 5 H), 2.19 (m, 1 H), 3.26 (s, 3 H), 4.38 (d, J=7.81 Hz, 2 H), 7.29 (dd, J=9.08, 2.05 Hz, 1 H), 7.50 (m, 1 H), 7.52 (m, 1 H) 7.55 (m, 3 H), 7.67 (m, 1 H), 7.83 (d, J=8.98 Hz, 1 H). MS (ESI) ($M+H$)⁺ = 438.2. Anal. Calcd for C₂₅H₃₁N₃O₂S+1.2 TFA+0.10 H₂O: C, 57.11; H, 5.67; N, 7.29. Found: C, 57.19; H, 5.74; N, 7.22.

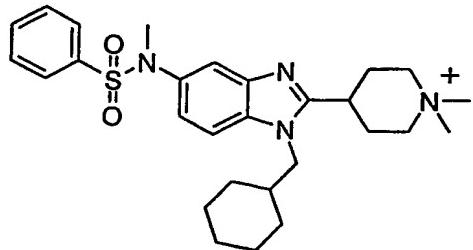
10 **Example 18 and 19**

Example 18: *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-*N*-methyl- benzenesulfonamide



15

Example 19: 4-[1-(cyclohexylmethyl)-5-[methyl(phenylsulfonyl)amino]-1*H*-benzimidazol-2-yl]-1,1-dimethyl- piperidinium



20 Following the procedure in Example 14: using *N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]- benzenesulfonamide (97.3 mg, 0.209 mmol), sodium hydride (18.4 mg, 60%, 0.459 mmol) and iodomethane/THF (1.0 M, 250 uL, 0.25 mmol) in THF (15 mL), the crude product was purified by reversed HPLC using 15-60% CH₃CN/H₂O to give the title compounds A and B as following:

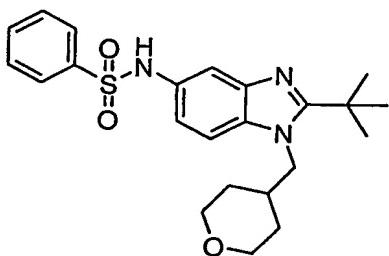
1) Compound A: N-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1H-benzimidazol-5-yl]-N-methyl- benzenesulfonamide. Yield: 36.8 mg (30%) The compound was converted to TFA salt as a white solid. $^1\text{HNMR}$ (400 MHz, CD_3OD): δ 1.10 (m, 2 H), 1.18 (m, 3 H), 1.55 (m, 2 H), 1.69 (m, 3 H), 1.81 (m, 1 H), 2.15 (m, 2 H), 2.38 (m, 2 H), 3.23 (s, 6 H), 3.46 (m, 1 H), 3.57 (m, 2 H), 3.66 (m, 2 H), 4.14 (d, $J=7.62$ Hz, 2 H), 7.13 (m, 1 H), 7.43 (m, 3 H), 7.51 (m, 2 H), 7.72 (m, 2 H). ($M+\text{H}$) $^+$ = 481.2. Anal. Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_2\text{S}+3.2 \text{TFA}+0.5 \text{H}_2\text{O}$: C, 46.94; H, 4.74; N, 6.56. Found: C, 46.97; H, 4.76; N, 6.51.

2) Compound B: 4-[1-(cyclohexylmethyl)-5-[methyl(phenylsulfonyl)amino]-1H-

10 benzimidazol-2-yl]-1,1-dimethyl- piperidinium. Yield: 41.1 mg (32%). TFA salt, white solid,. $^1\text{HNMR}$ (400 MHz, CD_3OD): δ 1.14 (m, 2 H), 1.23 (m, 3 H), 1.59 (m, 2 H), 1.72 (m, 3 H), 1.86 (m, 1 H), 2.18 (m, 2 H), 2.43 (m, 2 H), 3.25 (s, 3 H), 3.26 (s, 6 H), 3.46 (m, 1 H), 3.58 (m, 2 H), 3.69 (m, 2 H), 4.18 (d, $J=7.62$ Hz, 2 H), 7.11 (dd, $J=8.79, 1.95$ Hz, 1 H), 7.35 (d, $J=1.95$ Hz, 1 H), 7.50 (m, 1 H), 7.55 (m, 4 H), 7.66 (m, 1 H). MS (ESI) ($M+\text{H}$) $^+$: 495.2.

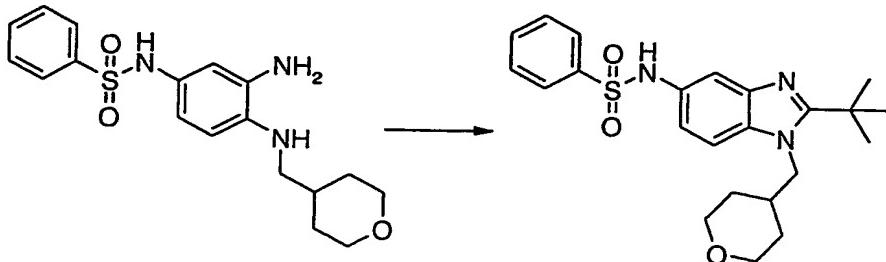
Example 20

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



20

Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide

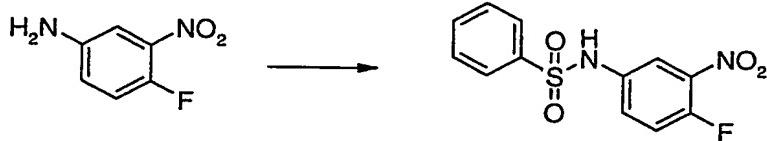


Catalytic DMAP in one portion and pivaloyl chloride (0.26 mL, 1.1 eq) were added dropwise sequentially to a stirring solution of *N*-[3-amino-4-[[*(tetrahydro-2*H*-pyran-4-yl)methyl]amino] phenyl]-benzenesulfonamide (705.2 mg, 1.95 mmol) (for preparation, see Steps B, C and D) in CH₂Cl₂ (100 mL) at 0°C. The solution was*

- 5 stirred for 2 hours, then the solvent was concentrated, and the residue was re-dissolved in AcOH (2 mL). The resulting solution was heated at 150°C for 1800 s using microwave irradiation and the solvent was then concentrated. The residue was re-dissolved in EtOAc, washed with 1N NaOH (2X) and brine and dried over anhydrous Na₂SO₄. Purification by MPLC using EtOAc followed by reversed-phase
 10 HPLC using 10-90% MeCN in H₂O afforded the title compound as a colourless solid (16.3 mg, 2% yield); ¹H NMR (400 MHz, CD₃OD) δ 1.46-1.55 (m, 4 H), 1.62 (s, 9 H), 2.25-2.35 (m, 1 H), 3.30-3.34 (m, 2 H), 3.88-3.92 (m, 2 H), 4.43 (d, *J*=7.42 Hz, 2 H), 7.22 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.60 (d, *J*=2.05 Hz, 1 H), 7.75-7.80 (m, 3 H); MS (ESI) (M+H)⁺ = 428.0.

15

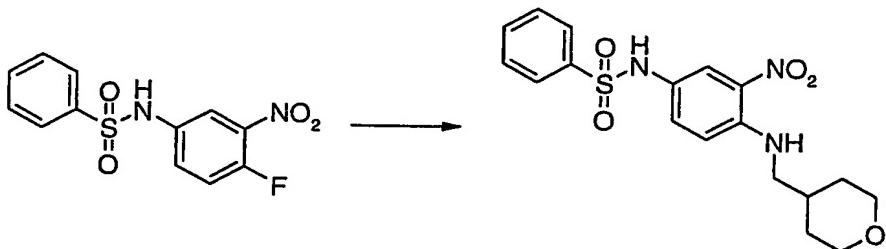
Step B. *N*-(4-fluoro-3-nitrophenyl)- benzenesulfonamide



Catalytic DMAP in one portion and benzene sulfonyl chloride (9.82 mL, 1.2 eq) dropwise were added sequentially to a stirring solution of 4-fluoro-3-nitroaniline (10

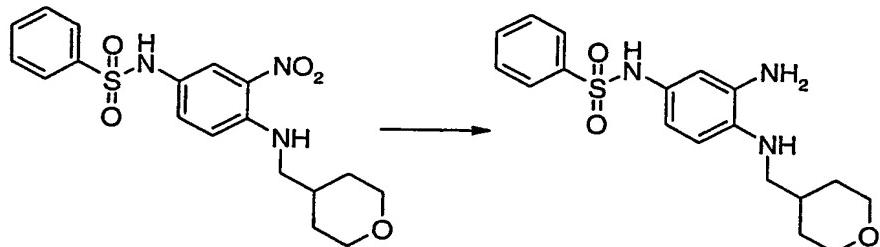
- 20 g, 64.1 mmol) in pyridine (52 mL) at 0°C. The solution was stirred at 0°C for 30 minutes and then warmed gradually to room temperature. After 3 hours at room temperature, the solution was diluted with EtOAc (15 mL) and was washed with water until the organic layer contained no pyridine by TLC (CH₂Cl₂). The solution was dried with anhydrous Na₂SO₄. Purification by MPLC using CH₂Cl₂ afforded the
 25 title compound as a pale yellow solid (13.6 g, 71% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.21 (dd, *J*=10.15, 8.98 Hz, 1 H), 7.32-7.36 (brs, 1 H), 7.44 (m, 1 H), 7.51 (m, 2 H), 7.62 (m, 1 H), 7.77 (dd, *J*=6.25, 2.93 Hz, 1 H), 7.82 (m, 2 H).

Step C. *N*-[3-nitro-4-[[*(tetrahydro-2*H*-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide*



4-Tetrahydropyranmethylamine (468 mg, 1.2 eq) in EtOH (0.5 mL) was added to a stirring solution of *N*-(4-fluoro-3-nitrophenyl)- benzenesulfonamide (1.0 g, 3.38 mmol) and triethylamine (0.47 mL, 1 eq) in EtOH:H₂O 4:1 (15 mL) at room temperature. The solution was heated at 60°C overnight, then cooled to room temperature. The cooled solution was poured into H₂O and was extracted (3X) with EtOAc. The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄. The crude product was purified by MPLC using 1:1 heptane:EtOAc to afford the title compound as a bright red solid (767.5 mg, 58%);
 10 ¹H NMR (400 MHz, CDCl₃) δ 1.41-1.46 (m, 2 H), 1.65-1.75 (m, 2 H), 1.90-1.98 (m, 1 H), 3.18-3.21 (m, 2 H), 3.39-3.45 (m, 2 H), 4.00-4.04 (m, 2 H), 6.61 (s, 1 H), 6.80 (d, J=9.18 Hz, 1 H), 7.38 (dd, J=9.28, 2.64 Hz, 1 H), 7.46-7.50 (m, 2 H), 7.56-7.60 (m, 1 H), 7.69 (d, J=2.54 Hz, 1 H), 7.73-7.75 (m, 2 H), 8.10 (m, 1 H).

15 Step D. *N*-[3-amino-4-[[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide

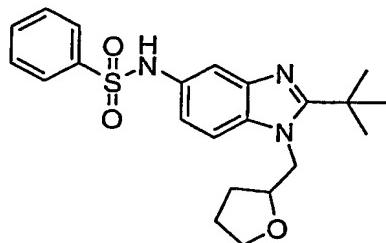


Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]-benzenesulfonamide (767.5 mg, 1.96 mmol)
 20 and a catalytic amount of 10% Pd/C in EtOAc (50 mL). LC/MS analysis indicated that the compound was of sufficient purity (>95%) to be used directly for Step A. Yield: 705.2 mg, 100%; ¹H NMR (400 MHz, CDCl₃) δ 1.33-1.44 (m, 2 H), 1.61-1.73 (m, 2 H), 1.81-1.88 (m, 1 H), 2.95 (d, J=6.64 Hz, 2 H), 3.37-3.43 (m, 5 H), 3.99 (dd, J=10.84, 3.42 Hz, 2 H), 6.27-6.31 (br. s., 1 H), 6.34-6.36 (m, 1 H), 6.42-6.44 (m, 1

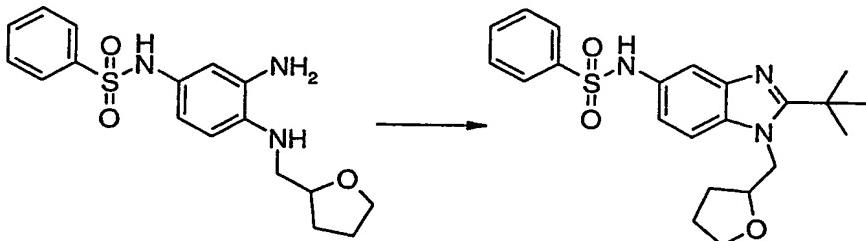
H), 6.58 (d, $J=2.34$ Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.55 (m, 1 H), 7.70-7.74 (m, 1 H).

Example 21

- 5 *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



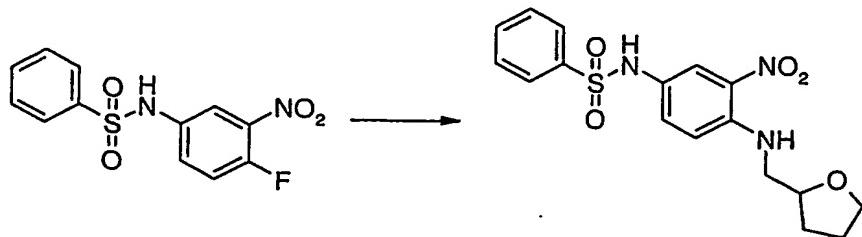
- 10 Step A. *N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-yl]-benzenesulfonamide



Following the procedure for Step A in Example 20, using *N*-[3-amino-4-[(tetrahydro-2-furanyl)methyl]amino] phenyl]-benzenesulfonamide (597.2 mg, 1.72 mmol) (for preparation, see the following steps B and C), CH₂Cl₂ (30 mL), catalytic DMAP and

- 15 pivaloyl chloride (0.23 mL, 1.1 eq), followed by AcOH (3 mL), the crude product was purified by MPLC using 4:1 EtOAc:hexanes, converted to the corresponding TFA salt and lyophilized. Yield of the title product as TFA salt: 182.3 mg (17%); ¹H NMR (400 MHz, CD₃OD) δ 1.60 (s, 9 H), 1.76-1.79 (m, 1 H), 1.89-2.04 (m, 2 H), 2.18-2.26 (m, 1 H), 3.64-3.69 (m, 1 H), 3.84-3.90 (m, 1 H), 4.28-4.34 (m, 1 H), 4.53-4.59 (m, 1 H), 4.66-4.71 (m, 1 H), 7.21 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (d, $J=1.95$ Hz, 1 H), 7.75-7.79 (m, 3 H); MS (ESI) (M+H)⁺ = 414.0.

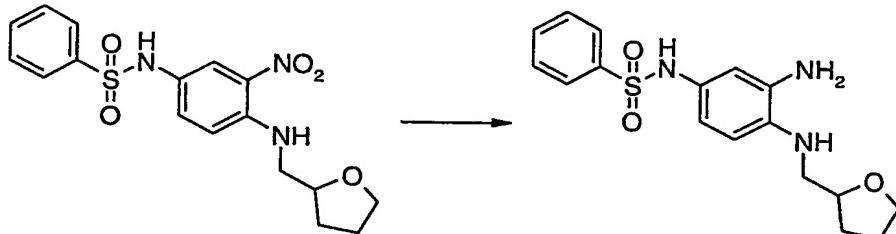
Step B. *N*-[3-nitro-4-[(tetrahydro-2-furanyl)methyl]amino]phenyl]-benzenesulfonamide



Following the procedure for Step C in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), tetrahydrofurylamine (0.42 mL, 1.2 eq), EtOH (12 mL) and H₂O (3 mL), the crude product was purified by MPLC using 1:1 heptane:EtOAc to afford the title compound as a bright red solid (749.7 mg, 59%); ¹H NMR (400 MHz, CDCl₃) δ 1.62-1.73 (m, 1 H), 1.94-2.13 (m, 3 H), 3.27-3.47 (m, 2 H), 3.80-3.98 (m, 2 H), 4.15-4.22 (m, 1 H), 6.51 (s, 1 H), 6.81 (d, *J*=9.18 Hz, 1 H), 7.35 (dd, *J*=8.98, 2.54 Hz, 1 H), 7.44-7.48 (m, 2 H), 7.55-7.59 (m, 1 H), 7.63 (d, *J*=2.73 Hz, 1 H), 7.69-7.72 (m, 2 H), 8.18-8.20 (m, 1 H).

10

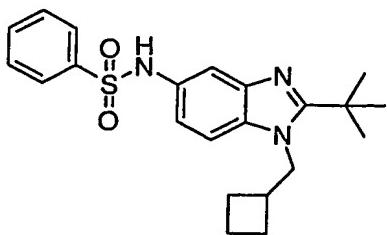
Step C. *N*-[3-amino-4-[[*(tetrahydro-2-furanyl)methyl*]amino]phenyl]-benzenesulfonamide



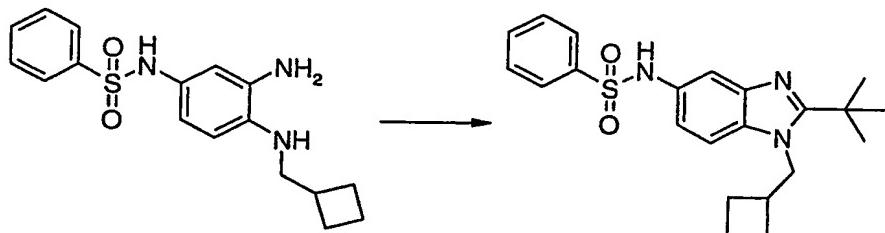
Following the procedure for Step E in Example 3, using *N*-[3-nitro-4-[(*tetrahydro-2-furanyl)methyl*]amino] phenyl-benzenesulfonamide (749.7 mg, 2 mmol) and a catalytic amount of 10% Pd/C in EtOAc (50 mL), LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 597.2 mg, 86%; ¹H NMR (400 MHz, CDCl₃) δ 1.61-1.70 (m, 2 H), 1.89-1.96 (m, 2 H), 2.01-2.09(m, 1 H), 2.97-3.02 (m, 1 H), 3.12-3.16 (m, 1 H), 3.34-3.59 (m, 3 H), 3.74-3.90 (m, 2 H), 6.28 (s, 1 H), 6.33 (dd, *J*=8.20, 2.34 Hz, 1 H), 6.44 (d, *J*=8.40 Hz, 1 H), 6.53 (d, *J*=2.34 Hz, 1 H), 7.39-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.68-7.72 (m, 2 H).

Example 22

***N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**

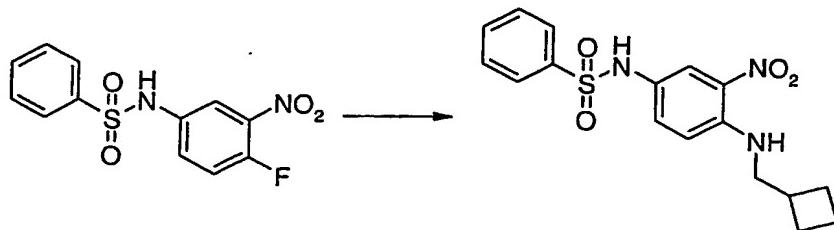


5 **Step A. *N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



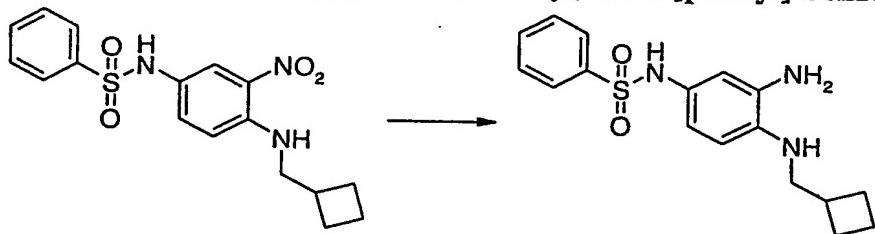
Following the procedure for Step A in Example 20, using *N*-[3-amino-4-[(cyclobutylmethyl)amino]phenyl]-benzenesulfonamide (763.8 mg, 2.30 mmol) (for preparation, see the following steps B and C), CH₂Cl₂ (40 mL), catalytic DMAP and 10 pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (9 mL), the crude product was purified by MPLC using 1:1 hexanes:EtOAc, followed by reversed-phase HPLC using 20-65% MeCN in H₂O. The compound was lyophilized to afford the title compound as its TFA salt (226.8 mg, 19%); ¹H NMR (400 MHz, CD₃OD) δ 1.60 (s, 9 H), 1.81-1.93 (m, 2 H), 2.01-2.07 (m, 4 H), 2.78-2.83 (m, 1 H), 4.55 (d, *J*=6.44 Hz, 2 H), 7.22 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (m, 1 H), 7.59 (dd, *J*=1.95, 0.59 Hz, 1 H), 7.70 (dd, *J*=8.98, 0.59 Hz, 1 H), 7.76-7.79 (m, 2 H); MS (ESI) 15 (*M*+H)⁺ = 398.0.

Step B. *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide



Following the procedure for Step C in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol), cyclobutylmethylamine (345.7 mg, 1.2 eq), EtOH (12 mL) and H₂O (5 mL). The crude product was purified by MPLC using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (857.7 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ 1.73-1.78 (m, 2 H), 1.88-2.00 (m, 2 H), 2.13-2.21 (m, 2 H), 2.62-2.73 (m, 1 H), 3.27-3.30 (m, 2 H), 6.44 (s, 1 H), 6.78 (d, *J*=9.18 Hz, 1 H), 7.36 (dd, *J*=9.08, 2.44 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.55-7.60 (m, 1 H), 7.66 (d, *J*=2.73 Hz, 1 H) 7.72-7.74 (m, 2 H), 7.93-7.98 (br s, 1 H).

10 **Step C. *N*-[3-amino-4-[(cyclobutylmethyl)amino]phenyl]-benzenesulfonamide**

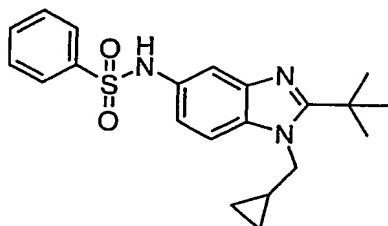


Following the procedure for Step E in Example 3, using *N*-[4-[(cyclobutylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (857.7 mg, 2.37 mmol) and a catalytic amount of 10% Pd/C in EtOAc (25 mL) and shaking for 48 h,

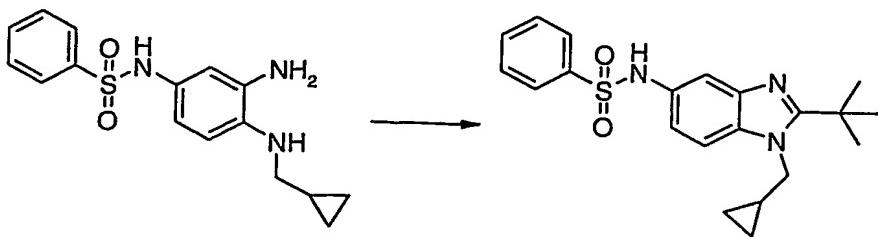
15 LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 763.8 mg, 97%; ¹H NMR (400 MHz, CDCl₃) δ 1.68-1.78 (m, 2 H), 1.86-1.98 (m, 2 H), 2.08-2.16 (m, 2 H), 2.54-2.62 (m, 1 H), 3.04 (d, *J*=7.42 Hz, 2 H), 3.11-3.42 (brs, 2 H), 6.28-3.31 (br. s., 1 H), 6.33 (dd, *J*=8.40, 2.34 Hz, 1 H), 6.43 (d, *J*=8.40 Hz, 1 H), 6.56 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.50-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

Example 23

N-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



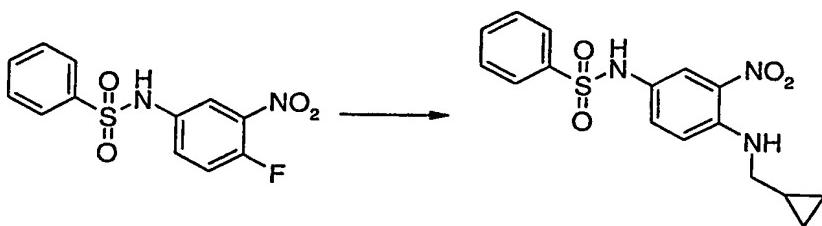
Step A. *N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



Following the procedure for Step A in Example 20, using *N*-[3-amino-4-

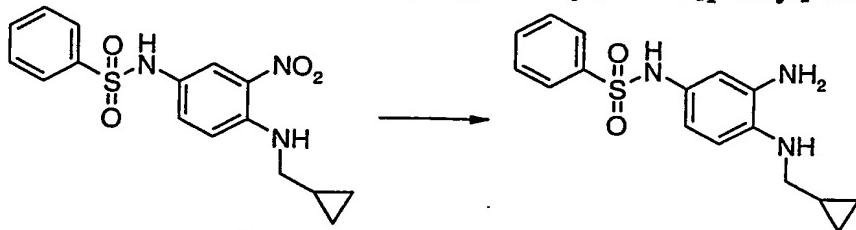
- 5 ((cyclopropylmethyl)amino)phenyl]-benzenesulfonamide (736.4 mg, 2.32 mmol) (for preparation, see the following steps B and C), CH₂Cl₂ (50 mL), catalytic DMAP and pivaloyl chloride (0.31 mL, 1.1 eq), followed by AcOH (10 mL), the crude product was purified by reversed-phase HPLC using 15-45% MeCN in H₂O. The compound was lyophilized to afford the title compound as its TFA salt (50 mg, 4.2%); ¹H NMR (400 MHz, CD₃OD) δ 0.57-0.61 (m, 2 H), 0.65-0.70 (m, 2 H), 1.22-1.25 (m, 1 H), 1.62 (s, 9 H), 4.47 (d, *J*=6.44 Hz, 2 H), 7.23 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.52-7.55 (m, 1 H), 7.62 (d, *J*=1.95 Hz, 1 H), 7.74 (d, *J*=8.98 Hz, 1 H), 7.73-7.78 (m, 2 H); MS (ESI) (M+H)⁺ = 384.0.

15 **Step B. *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide**



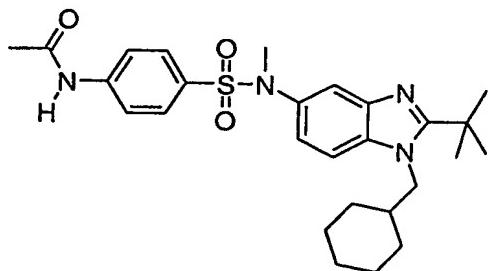
Following the procedure for Step C in Example 20, using *N*-(4-fluoro-3-nitrophenyl)-benzenesulfonamide (1.0 g, 3.38 mmol) and cyclopropylmethylamine (0.4 mL, 1.2 eq) in EtOH (12 mL) and H₂O (5 mL). The crude product was purified by MPLC

- 20 using 7:3 hexanes:EtOAc to afford the title compound as a bright orange solid (828.3 mg, 71%); ¹H NMR (400 MHz, CDCl₃) δ 0.29-0.33 (m, 2 H), 0.63-0.67 (m, 2 H), 1.14-1.19 (m, 1 H), 3.13 (dd, *J*=7.03, 4.88 Hz, 2 H), 6.42 (s, 1 H), 6.76 (d, *J*=9.37 Hz, 1 H), 7.36 (dd, *J*=9.18, 2.54 Hz, 1 H), 7.45-7.49 (m, 2 H), 7.56-7.59 (m, 1 H), 7.67 (d, *J*=2.54 Hz, 1 H), 7.71-7.74 (m, 2 H), 8.07-8.13 (m, 1 H).

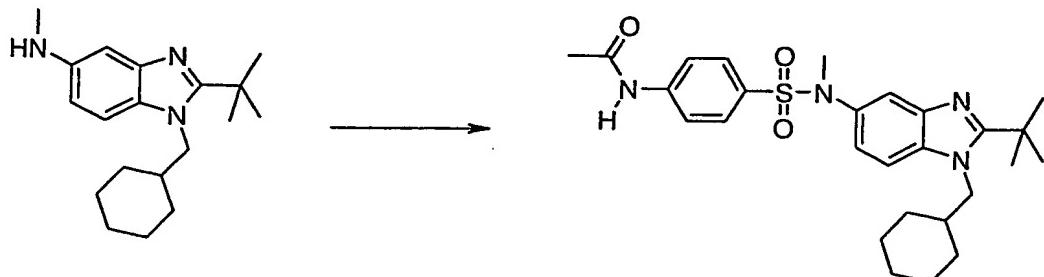
Step C. *N*-[3-amino-4-[(cyclopropylmethyl)amino]phenyl]-benzenesulfonamide

Following the procedure for Step E in Example 3, using *N*-[4-[(cyclopropylmethyl)amino]-3-nitrophenyl]-benzenesulfonamide (828.3 mg, 2.38 mmol), a catalytic amount of 10% Pd/C in EtOAc (30 mL). LC/MS analysis indicated that the title compound was of sufficient purity (>95%) to be used directly for the next step. Yield: 736.4 mg, 100%; ¹H NMR (400 MHz, CDCl₃) δ 0.20-0.24 (m, 2 H), 0.53-0.58 (m, 2 H), 1.08-1.12 (m, 1 H), 2.87 (d, *J*=7.03 Hz, 2 H), 3.28-3.48 (br. s., 2 H), 6.27-6.31 (br. s., 1 H), 6.31-6.34 (m, 1 H), 6.39-6.41 (m, 1 H), 6.57 (d, *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.49-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

5 indicated that the title compound was of sufficient purity (>95%) to be used directly
for the next step. Yield: 736.4 mg, 100%; ¹H NMR (400 MHz, CDCl₃) δ 0.20-0.24
(m, 2 H), 0.53-0.58 (m, 2 H), 1.08-1.12 (m, 1 H), 2.87 (d, *J*=7.03 Hz, 2 H), 3.28-3.48
(br. s., 2 H), 6.27-6.31 (br. s., 1 H), 6.31-6.34 (m, 1 H), 6.39-6.41 (m, 1 H), 6.57 (d,
10 *J*=2.34 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.49-7.54 (m, 1 H), 7.69-7.71 (m, 2 H).

Example 24***N*-(4-{{[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl}phenyl) acetamide**

15

Step A. *N*-(4-{{[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl}phenyl) acetamide

2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.133 mmol) (for preparation, see the following steps B, C, D, E and F) and 4-acetamidobenzene sulfonyl chloride (37 mg, 0.160 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The solvent
 5 was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 63 mg (78%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.61 (m, 3 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 1 H), 2.11 (s, 3 H), 3.22 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.29 (dd, J=9.08, 2.05 Hz, 1 H), 7.42 (d, J=8.98 Hz, 2 H), 7.50 (d, J=1.56 Hz, 1 H), 7.68 (d, J=8.98 Hz, 2 H), 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 497.2; Anal. Calcd for C₂₇H₃₆N₄O₃S + 1.4 TFA + 0.4 H₂O: C, 53.94; H, 5.80; N, 8.44. Found: C, 53.98; H, 5.79; N, 8.50.

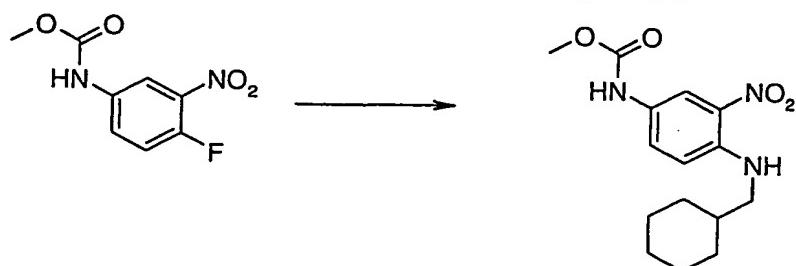
Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate



15

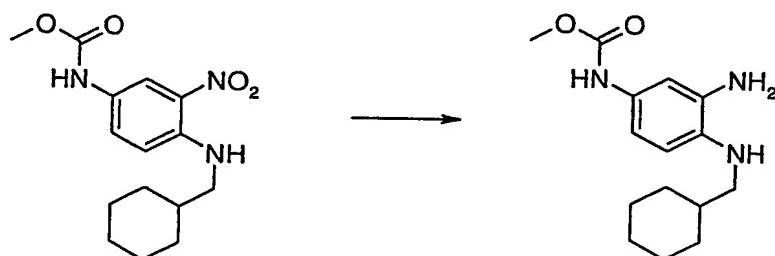
Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M
 20 HCl, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3 H), 7.02 (s, 1 H), 7.23 (m, 1 H), 7.72 (d, J=8.59 Hz, 1 H), 8.17 (dd, J=6.35, 2.64 Hz, 1 H).

25 Step C. Methyl {4-[cyclohexylmethyl]amino}-3-nitrophenyl carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.04 (ddd, J = 24.02, 12.11, 2.93 Hz, 2H); 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd, J = 6.44, 5.66 Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, J = 9.37 Hz, 1H), 7.63 (m, 1H), 8.05 (d, J = 2.54 Hz, 1H), 8.09 (m, 1H).

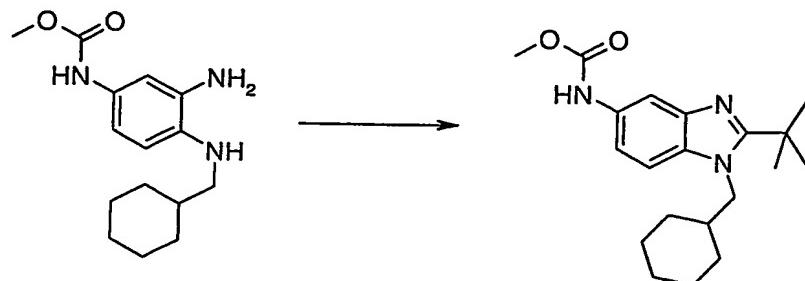
Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate



Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent was evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%); MS (ESI) (M+H)⁺ 277.9.

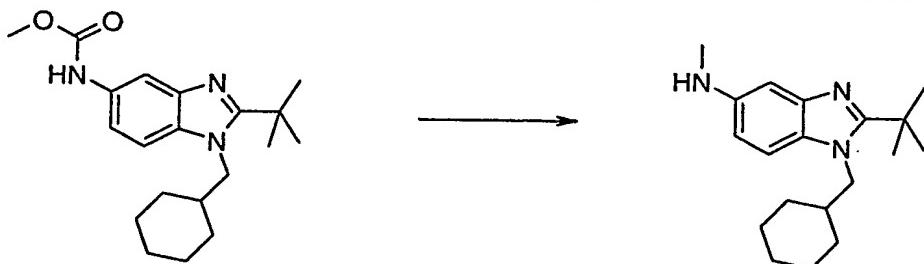
20

Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The residue was divided in two portions and each of them dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The two tubes were combined and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s, 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-N-methyl-1*H*-benzimidazol-5-amine

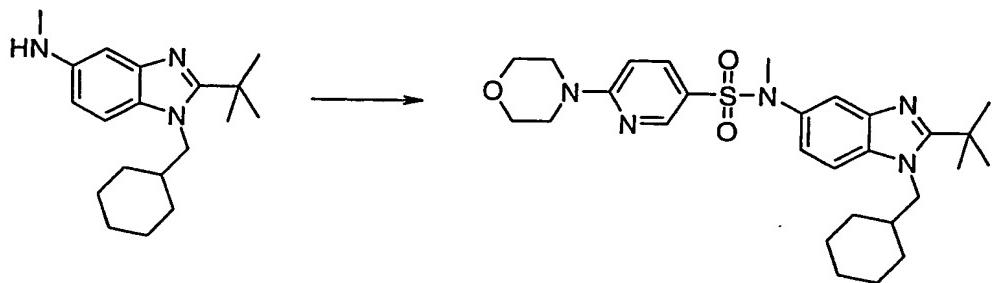


Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution stirred at 0°C for 15min. LiAlH₄ (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (s, 2 H) 1.17 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 2 H) 1.67 (m, 2 H) 1.72 (m, 2 H) 2.02 (m, 1 H) 2.87 (s,

3 H) 4.06 (d, $J=7.62$ Hz, 2 H) 6.60 (dd, $J=8.69, 2.25$ Hz, 1 H) 7.00 (d, $J=1.76$ Hz, 1 H) 7.12 (d, $J=8.59$ Hz, 1 H).

Example 25

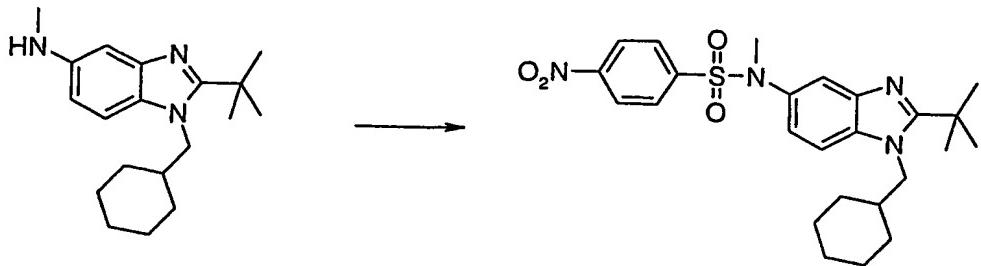
- 5 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-6-morpholin-4-ylpyridine-3-sulfonamide



- Following the procedure for Step A in Example 24, using 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (39 mg, 0.130 mmol), 6-morpholino-3-pyridinesulfonyl chloride (41 mg, 0.156 mmol) and DMAP (catalytic) in 2 mL of DCM. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 11 mg (13%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.61 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.08 (s, 1 H), 3.23 (s, 3 H), 3.60 (m, 4 H), 3.71 (m, 4 H), 4.42 (d, $J=7.62$ Hz, 2 H), 6.77 (d, $J=8.59$ Hz, 1 H), 7.34 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.57 (m, 2 H), 7.83 (d, $J=8.98$ Hz, 1 H), 8.08 (d, $J=1.95$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 526.0; Anal. Calcd for C₂₈H₃₉N₅O₃S + 1.7 TFA + 0.5 H₂O: C, 51.77; H, 5.77; N, 9.61. Found: C, 51.76; H, 5.75; N, 9.69.
- 20

Example 26

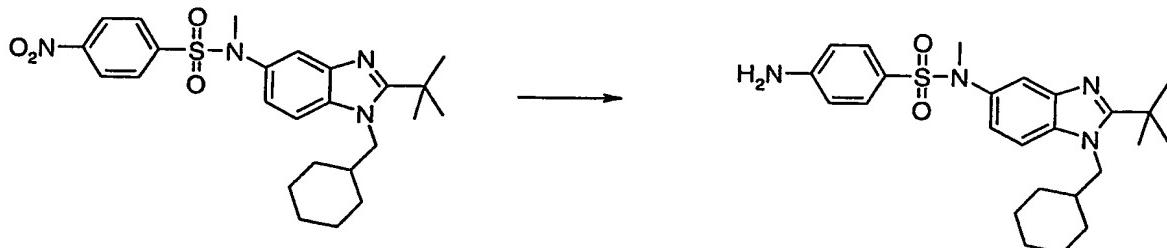
- N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide



Following the procedure for Step A in Example 24, using 2-*tert*-butyl-1-(cyclohexylmethyl)-N-methyl-1*H*-benzimidazol-5-amine (253 mg, 0.845 mmol), 4-nitrobenzenesulfonyl chloride (245 mg, 1.10 mmol) and DMAP (catalytic) in 20mL of DCM. The solution was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography on silica gel using 2:1 / hexanes:EtOAc as eluent to afford the title product. Yield: 380 mg (93%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.09 (m, 2 H) 1.21 (m, 3 H) 1.54 (s, 9 H) 1.64 (m, 1 H) 1.67 (m, 1 H) 1.71 (m, 1 H) 1.76 (m, 2 H) 2.03 (m, 1 H) 3.27 (s, 3 H) 4.12 (d, *J*=7.23 Hz, 2 H) 7.18 (m, *J*=8.98 Hz, 2 H) 7.30 (d, *J*=8.98 Hz, 1 H) 7.77 (d, *J*=9.18 Hz, 2 H) 8.30 (d, *J*=9.18 Hz, 2 H).

Example 27

4-Amino-N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-N-methylbenzenesulfonamide



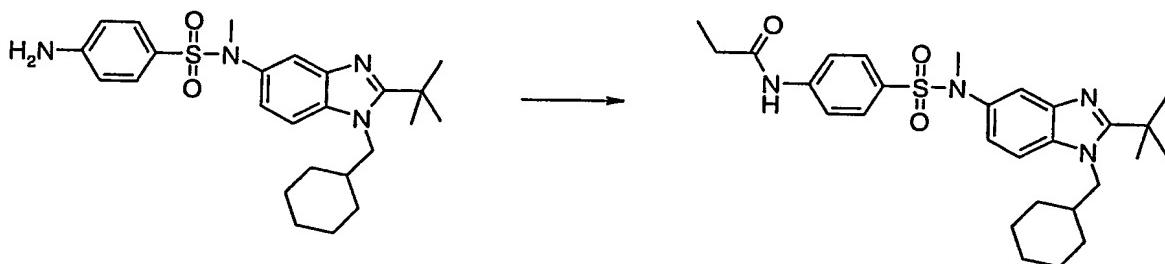
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide (375mg, 0.774 mmol) was dissolved in 20 mL of EtOH containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H₂ atmosphere (40 psi) at rt for 3h. The solution was filtered through celite and the solvent was concentrated. Yield: 332 mg (94%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.22 (m, 6 H) 1.60 (m, 1 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 3.17 (s, 3 H) 4.42 (d, *J*=7.42 Hz, 2 H) 6.56 (d,

$J=8.79$ Hz, 2 H) 7.14 (d, $J=8.79$ Hz, 2 H) 7.32 (dd, $J=8.98$, 1.95 Hz, 1 H) 7.49 (d, $J=1.95$ Hz, 1 H) 7.81 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 455.0; Anal. Calcd for $C_{25}H_{34}N_4O_2S + 1.5$ TFA + 0.4 H_2O : C, 53.14; H, 5.78; N, 8.85. Found: C, 53.10; H, 5.67; N, 8.92.

5

Example 28

N-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)propanamide

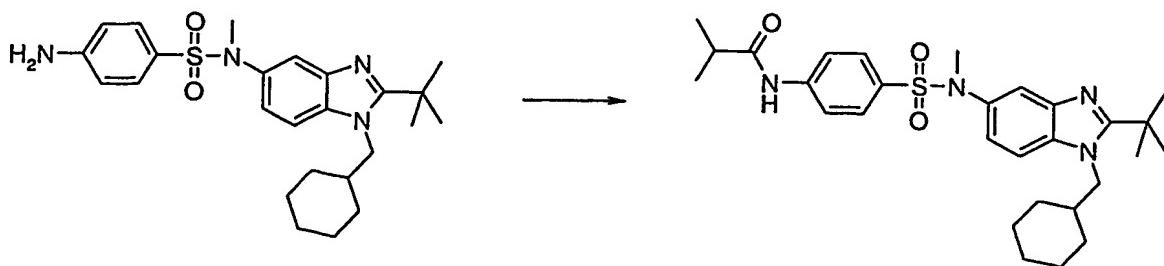


10

4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.110 mmol) and propionyl chloride (0.012 mL, 0.143 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at 15 rt for 12h. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 68mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.16 (t, $J=7.62$ Hz, 3 H) 1.21 (m, 5 H) 1.60 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.07 (m, 1 H) 2.38 (q, $J=7.62$ Hz, 2 H) 3.22 (s, 3 H) 4.42 (d, $J=7.62$ Hz, 2 H) 7.29 (dd, $J=9.08$, 2.05 Hz, 1 H) 7.42 (d, $J=8.98$ Hz, 2 H) 7.49 (d, $J=1.76$ Hz, 1 H) 7.69 (d, $J=8.98$ Hz, 2 H) 7.81 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 511.2; Anal. Calcd for $C_{28}H_{38}N_4O_3S + 1.5$ TFA + 0.2 H_2O : C, 54.33; H, 5.87; N, 8.18. Found: C, 54.32; H, 5.84; N, 8.25.

25 **Example 29**

N-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-methylpropanamide

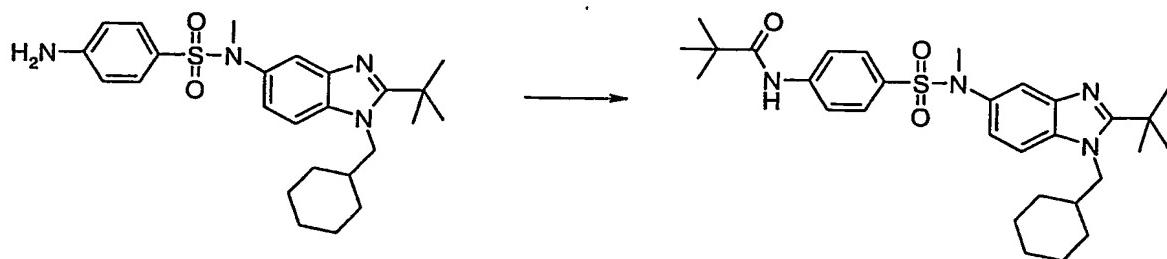


Following the procedure for Example 28, using 4-amino-N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg,

- 5 0.110 mmol), isobutyryl chloride (0.015 mL, 0.143 mmol) and a catalytic amount of DMAP in 3mL of DCM. Yield: 73mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.15 (d, J=6.83 Hz, 6 H) 1.21 (m, 5 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 2.61 (dt, J=13.82, 6.86 Hz, 1 H) 3.23 (s, 3 H) 4.42 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=8.98, 1.95 Hz, 1 H) 7.42 (d, J=8.98 Hz, 2 H) 7.50 (d, J=1.95 Hz, 1 H) 7.71 (d, J=8.98 Hz, 2 H) 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 525.3; Anal. Calcd for C₂₉H₄₀N₄O₃S + 1.7 TFA + 0.3 H₂O: C, 53.75; H, 5.89; N, 7.74. Found: C, 53.75; H, 5.87; N, 7.73.

Example 30

- 15 *N*-(4-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl)phenyl)-2,2-dimethylpropanamide



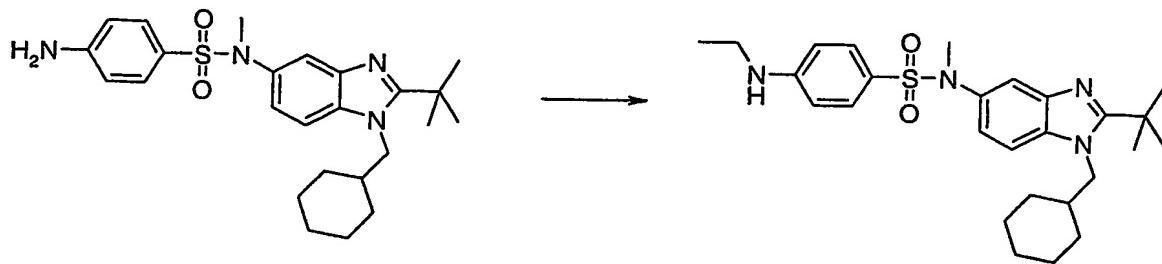
Following the procedure for Example 28, using 4-amino-N-[2-*tert*-butyl-1-

- 20 (cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50 mg, 0.110 mmol), trimethylacetyl chloride (0.018 mL, 0.143 mmol) and a catalytic amount of DMAP in 3mL of DCM. Yield: 76mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H) 1.26 (s, 9 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.07 (m, 1 H) 3.23 (s, 3 H) 4.42 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=9.08, 2.05 Hz, 1 H) 7.42 (d, J=8.98 Hz, 2 H) 7.49 (d, J=1.76 Hz, 1 H) 7.73 (d,

$J=8.98$ Hz, 2 H) 7.82 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 539.2; Anal. Calcd for $C_{30}H_{42}N_4O_3S + 1.4$ TFA + 0.5 H₂O: C, 55.69; H, 6.33; N, 7.92. Found: C, 55.70; H, 6.31; N, 7.92.

5 Example 31

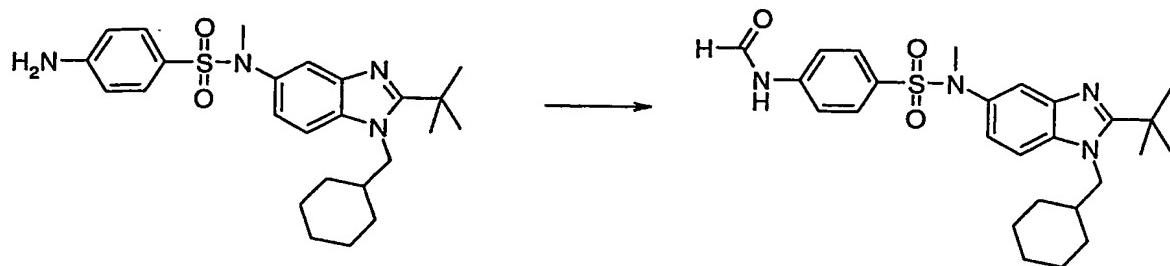
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(ethylamino)-N-methylbenzenesulfonamide



- 10 4-Amino-N-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (55 mg, 0.121 mmol), cesium carbonate (78 mg, 0.242 mmol) and ethyl iodide (0.011 mL, 0.133 mmol) were dissolved in 1 mL of DMF in a sealed tube flushed with nitrogen. The solution was heated at 125°C in a Personal Chemistry SmithSynthesizer microwave instrument for 10 min. Another 0.133 mmol (0.011 mL) of ethyl iodide was added and the solution was heated for another 10 min. This procedure was then repeated 3 more times. The solvent was then concentrated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. . The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 39 mg (54%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.19 (t, $J=7.23$ Hz, 3 H) 1.23 (m, 5 H) 1.62 (m, 2 H) 1.64 (s, 9 H) 1.67 (m, 1 H) 1.75 (m, 2 H) 2.08 (m, 1 H) 3.10 (q, $J=7.23$ Hz, 2 H) 3.17 (s, 3 H) 4.43 (d, $J=7.62$ Hz, 2 H) 6.52 (d, $J=8.98$ Hz, 2 H) 7.18 (d, $J=8.98$ Hz, 2 H) 7.32 (dd, $J=8.98$, 1.95 Hz, 1 H) 7.51 (d, $J=2.15$ Hz, 1 H) 7.81 (d, $J=8.98$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 483.3; Anal. Calcd for $C_{27}H_{38}N_4O_2S + 1.8$ TFA: C, 53.43; H, 5.83; N, 8.14. Found: C, 53.51; H, 5.81; N, 8.13.

Example 32

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(formylamino)-*N*-methylbenzenesulfonamide



5

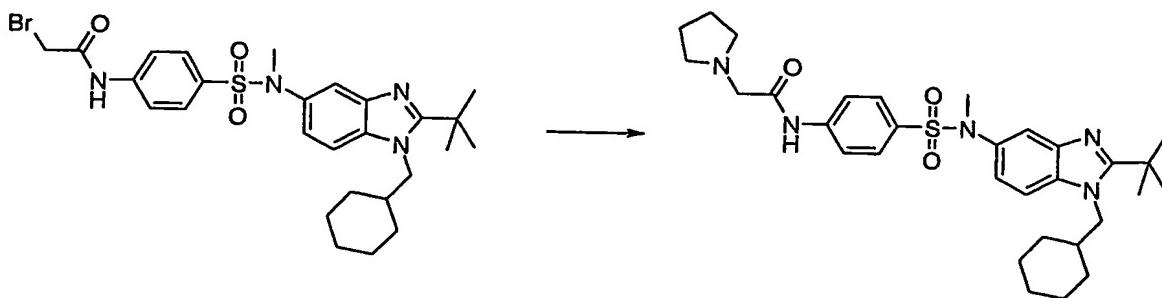
4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (45 mg, 0.099 mmol), was heated in 1 mL of formic acid in a sealed tube at 125°C for 15 min using a Personal Chemistry SmithSynthesizer

10 microwave instrument. The solvent was concentrated and the product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 61 mg (99%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.21 (m, 5 H), 1.62 (m, 2 H), 1.64 (s, 9 H), 1.67 (m, 1 H), 1.75 (m, 2 H), 2.08 (m, 1 H), 3.23 (s, 3 H), 4.42 (d, J=7.62 Hz, 2 H), 7.29 (dd, J=8.98, 15 1.95 Hz, 1 H), 7.45 (d, J=8.98 Hz, 2 H), 7.50 (d, J=1.76 Hz, 1 H), 7.70 (d, J=8.79 Hz, 2 H), 7.82 (d, J=8.98 Hz, 1 H), 8.31 (s, 1 H); MS (ESI) (M+H)⁺ 483.0; Anal. Calcd for C₂₆H₃₄N₄O₃S + 1.4 TFA + 0.5 H₂O: C, 53.11; H, 5.63; N, 8.60. Found: C, 53.02; H, 5.62; N, 8.71.

20 **Example 33**

N-(4-{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-pyrrolidin-1-ylacetamide

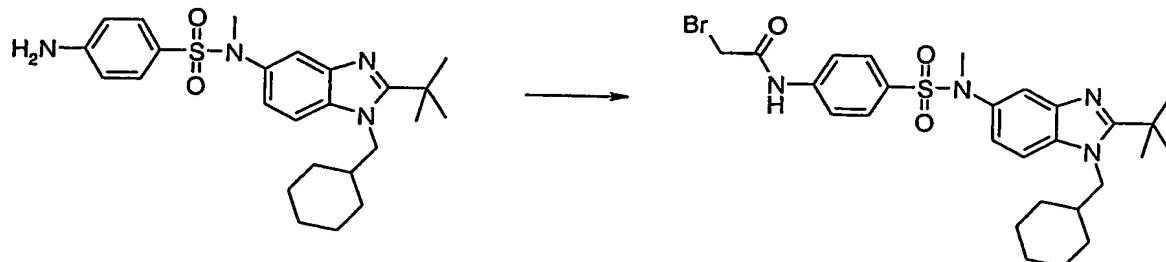
STEP A:



2-Bromo-N-(4-{[2-tert-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide (42 mg, 0.0730 mmol) and pyrrolidine (0.030 mL, 0.365 mmol)

- 5 were dissolved in 1 mL of DMF in a sealed tube. The solution was heated at 125°C in a Personal Chemistry SmithSynthesizer microwave instrument for 15 min. The solvent was concentrated. The residue was dissolved in EtOAc and was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the crude product was 10 purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 51 mg (88%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.63 (m, 2 H) 1.67 (s, 11 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.09 (m, 2 H) 2.17 (m, 2 H) 3.19 (m, 1 H) 3.27 (s, 3 H) 3.78 (m, 1 H) 4.27 (s, 2 H) 4.44 (d, J=7.62 Hz, 2 H) 7.28 (dd, J=8.98, 1.95 Hz, 1 H) 7.53 (d, J=8.98 Hz, 2 H) 7.59 (d, J=1.76 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 566.2; Anal. Calcd for C₃₁H₄₃N₅O₃S + 2.7 TFA + 0.4 H₂O: C, 49.63; H, 5.32; N, 7.95. Found: C, 49.63; H, 5.33; N, 7.93.

STEP B: 2-Bromo-N-(4-{[2-tert-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide



4-Amino-N-[2-tert-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-N-methylbenzenesulfonamide (155 mg, 0.341 mmol) was dissolved in 5 mL of DCM

containing a catalytic amount of DMAP. Bromoacetyl chloride (0.035 mL, 0.409 mmol) was added and the solution was stirred at rt for 3h. The solution was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄.

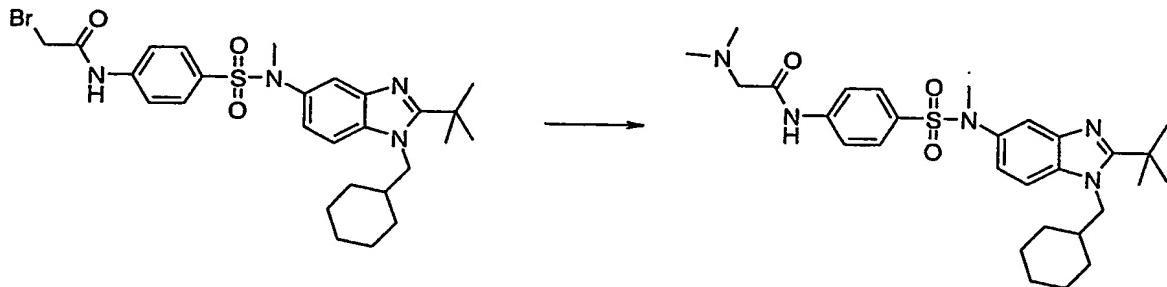
The crude product was purified by flash chromatography on silica gel using 50-75%

- 5 EtOAc in hexanes as eluent to afford the title product. Yield: 175 mg (89%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.09 (m, 1H) 1.12 (m, 1H) 1.15 (m, 1H) 1.19 (d J=8.59 Hz, 2H) 1.54 (s, 9H) 1.65 (m, 1H) 1.68 (m, 1H) 1.72 (m, 1H) 1.75 (m, 2H) 2.04 (m, 1H) 3.21 (d, J=1.17 Hz, 3H) 4.04 (s, 1H) 4.12 (m, 2H) 4.22 (s, 1H) 7.20 (m, 1H) 7.23 (m, 1H) 7.28 (m, 1H) 7.57 (m, 2H) 7.66 (t, J=8.49 Hz, 2H) 8.44 (d, J=8.40 Hz, 1H).

10

Example 34

*N*¹-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-*N*²,*N*²-dimethylglycinamide

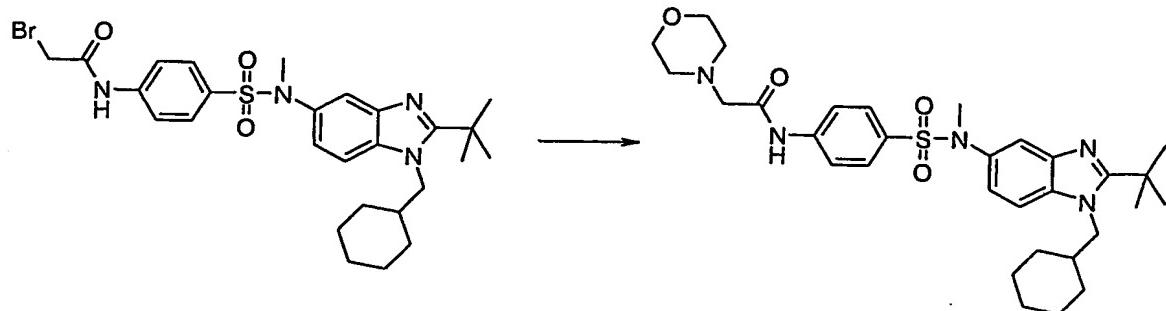


15

Following the procedure for Example 33, using 2-bromo-*N*-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide (40 mg, 0.0695 mmol), dimethylamine hydrochloride (0.030 mg, 0.348 mmol) and DIPEA (0.060 mL, 0.348 mmol) in 1 mL of DMF. Yield: 35 mg (77%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.64 (m, 2 H) 1.67 (s, 9 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.10 (m, 1 H) 3.00 (s, 6 H) 3.27 (s, 3 H) 4.18 (s, 2 H) 4.45 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=8.98, 1.95 Hz, 1 H) 7.54 (d, J=8.98 Hz, 2 H) 7.60 (d, J=1.76 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.82 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 540.3; Anal. Calcd for C₂₉H₄₁N₅O₃S + 2.9 TFA + 0.5 H₂O: C, 47.53; H, 5.15; N, 7.96. Found: C, 47.57; H, 5.11; N, 7.99.

Example 35

N-(4-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-morpholin-4-ylacetamide



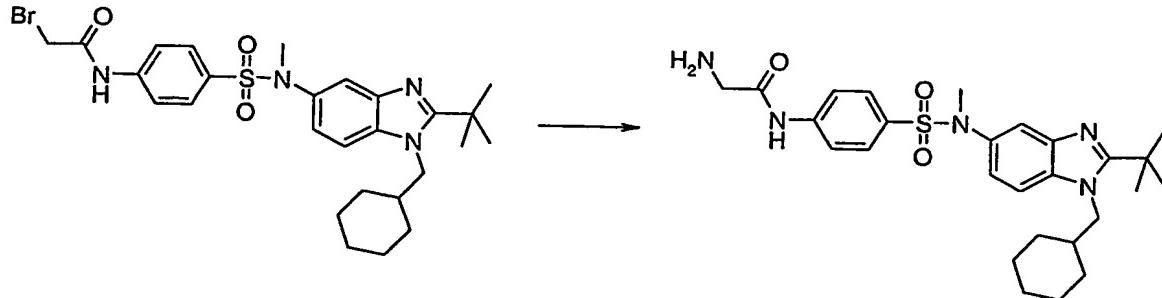
5

Following the procedure for Example 33, using 2-bromo-*N*-(4-{{[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide (56 mg, 0.0973 mmol) and morpholine (0.045 mL, 0.486 mmol) in 1 mL of DMF. Yield: 15mg (26%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H) 1.64 (m, 2 H) 1.67 (s, 9 H) 1.70 (m, 1 H) 1.78 (m, 2 H) 2.11 (m, 1 H) 3.27 (s, 3 H) 3.42 (m, 4 H) 3.96 (m, 4 H) 4.17 (s, 2 H) 4.45 (d, J=7.62 Hz, 2 H) 7.29 (dd, J=8.98, 2.15 Hz, 1 H) 7.54 (d, J=9.18 Hz, 2 H) 7.60 (d, J=1.56 Hz, 1 H) 7.77 (d, J=8.98 Hz, 2 H) 7.83 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 582.2; Anal. Calcd for C₃₁H₄₃N₅O₄S + 3.2 TFA + 0.2 H₂O: C, 47.27; H, 4.94; N, 7.37. Found: C, 47.23; H, 4.92; N, 7.49.

15

Example 36

*N*¹-(4-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)glycinamide



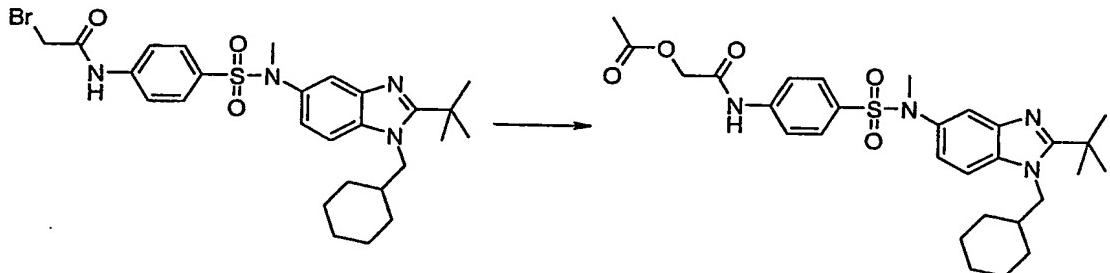
20

Following the procedure for Example 33, using 2-bromo-*N*-(4-{{[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide (37 mg, 0.0608 mmol) and ammonium hydroxide (28% aqueous) (0.5 mL,

excess) in 1 mL of DMF. Yield: 28mg (74%); ^1H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.27 (s, 3 H), 3.89 (s, 2 H), 4.44 (d, $J=7.62$ Hz, 2 H), 7.30 (dd, $J=8.98, 1.95$ Hz, 1 H), 7.53 (d, $J=9.18$ Hz, 2 H), 7.58 (d, $J=1.76$ Hz, 1 H), 7.76 (d, $J=8.98$ Hz, 2 H), 5 7.82 (d, $J=9.18$ Hz, 1 H); MS (ESI) ($M+\text{H}$)⁺ 512.0; Anal. Calcd for C₂₇H₃₇N₅O₃S + 2.6 TFA + 1.6 H₂O: C, 46.21; H, 5.15; N, 8.37. Found: C, 46.22; H, 5.09; N, 8.43.

Example 37

- 10 2-[(4-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl}phenyl)amino]-2-oxoethyl acetate

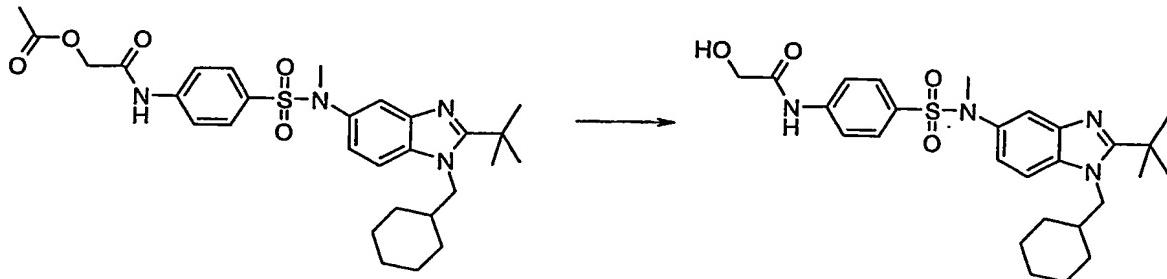


Following the procedure for Example 33, using 2-bromo-N-(4-{{[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl)phenyl)acetamide (50 mg, 0.0869 mmol) and sodium acetate (35 mg, 0.434 mmol) in 2 mL of

- 15 DMF. The product was used directly for the next step without any further purification. Yield: 48 mg (99%); MS (ESI) ($M+\text{H}$)⁺ 555.2.

Example 38

- 20 N-(4-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl)phenyl)-2-hydroxyacetamide

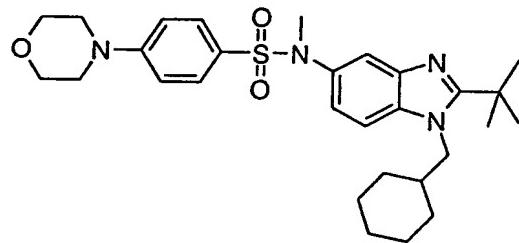


2-[(4-{{[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino}sulfonyl)phenyl]amino]-2-oxoethyl acetate (48 mg, 0.0869 mmol)

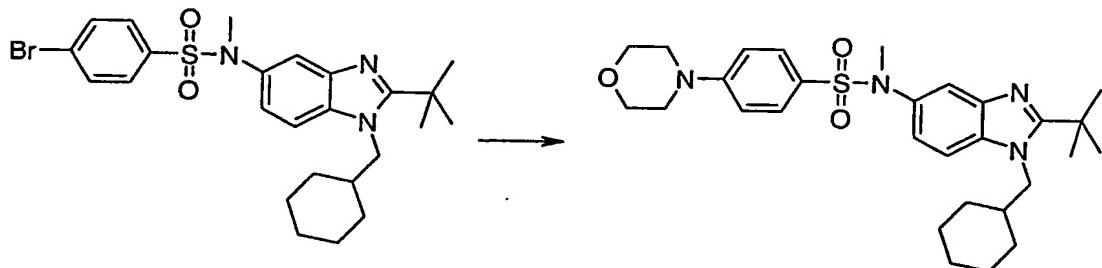
was refluxed in 2 mL of EtOH containing 1M LiOH (0.5 mL, excess) for 2h. The solvent was concentrated and the residue was dissolved in EtOAc. The organic phase was washed with saturated NaHCO₃ aqueous solution, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the crude product was purified by 5 reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 16 mg (29%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.24 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.10 (m, 1 H), 3.27 (s, 3 H), 4.13 (s, 2 H), 4.45 (d, J=7.62 Hz, 2 H), 10 7.31 (dd, J=9.08, 2.05 Hz, 1 H), 7.49 (d, J=8.79 Hz, 2 H), 7.53 (d, J=1.95 Hz, 1 H), 7.83 (m, 3 H); MS (ESI) (M+H)⁺ 513.0.

Example 39

N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-morpholinyl)-benzenesulfonamide



15 Step A. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-morpholinyl)-benzenesulfonamide



20 4-Bromo-*N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide (for preparation, see the following steps B, C, D, E, F, G and H) (80.1 mg, 0.154 mmol), morpholine (16 ul, 15.7 mg, 0.18 mmol), KOBu-t (20.2 mg, 0.21 mmol), Pd(dba)₂ (12.9 mg, 0.014 mmol) and BINAP (11.5 mg, 0.018 mmol) in toluene (3 mL) were placed in a sealed tube. The mixture was heated at 170°C in a Personal Chemistry SmithSynthesizer microwave instrument for 30 min,

diluted with EtOAc (50 mL), brine (2x10 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated and the crude product was purified by reversed-phase HPLC using 20-70% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA. Yield: 45.3 mg (46%); ¹H NMR (400 MHz, METHANOL-D₄) δ

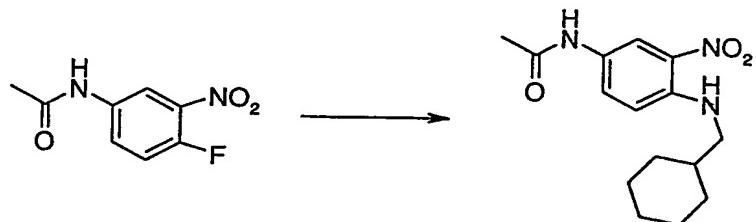
- 5 1.25 (m, 5 H), 1.63 (m, 2 H), 1.67 (s, 9 H), 1.72 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.23 (s, 3 H), 3.28 (m, 4 H), 3.80 (m, 4 H), 4.45 (d, J=7.62 Hz, 2 H), 6.96 (m, 2 H), 7.33 (dd, J=9.08, 2.05 Hz, 1 H), 7.37 (m, 2 H), 7.54 (d, J=1.76 Hz, 1 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 525.3.

10 **Step B. N-(4-fluoro-3-nitrophenyl)acetamide**



4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added portionwise to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title 15 compound (42.0 g, 70%). ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, J=6.44, 2.73 Hz, 1 H).

Step C. N-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}acetamide



- 20 Cyclohexylmethylamine (2.86 mL, 2.49 g, 22.0 mmol) was added to a mixture of N-(4-fluoro-3-nitrophenyl)acetamide (3.96 g, 20.0 mmol) and sodium carbonate (4.66 g, 44 mmol) in EtOH (50 mL) at room temperature. The reaction mixture was heated for 48 h at 60 °C, and diluted with H₂O (800 mL). The orange solid was precipitated out and collected to give the title product (6.60 g, 100%). MS (ESI) (M+H)⁺: 292.3.

25

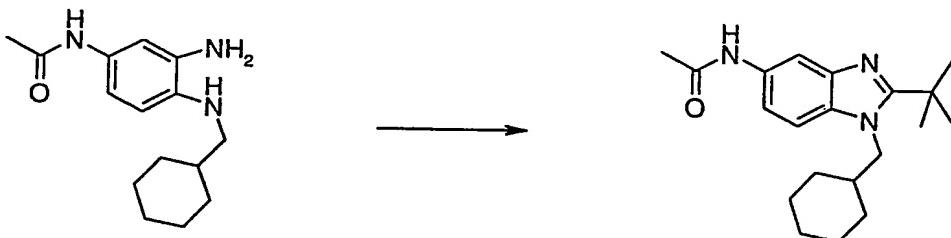
Step D. N-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}acetamide



(*N*-(4-[(Cyclohexylmethyl)amino]-3-nitrophenyl)acetamide) was hydrogenated in ethyl acetate (300 mL) catalyzed by 10% Pd/C (0.5 g) at 20-30 psi H₂ in Parr shaker for 4.5 h at room temperature. After filtration through celite and concentration, 5.08 g
 5 (97%) of a purple solid was obtained, which was used in the next step without purification. ¹H NMR (400 MHz, CDCl₃): δ 1.00 (m, 2 H), 1.24 (m, 3 H), 1.59 (m, 2 H), 1.72 (m, 2 H), 1.84 (m, 2 H), 2.13 (s, 3 H), 2.91 (d, J=6.64 Hz, 2 H), 3.37 (s broad, 3 H), 6.56 (d, J=8.40 Hz, 1 H), 6.69 (dd, J=8.30, 2.25 Hz, 1 H), 6.98 (s, 1 H), 7.12 (d, J=2.34 Hz, 1 H); MS (ESI) (M+H)⁺: 262.3.

10

Step E. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide



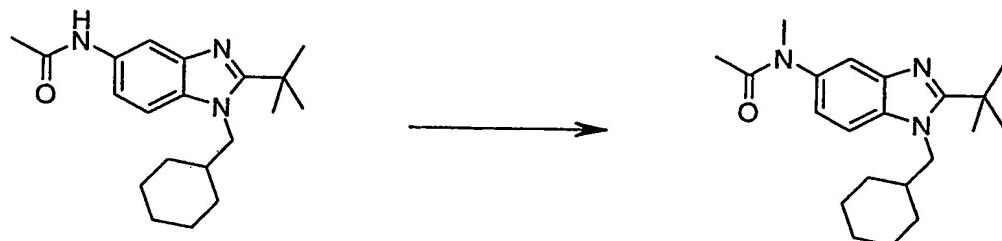
DMAP (0.15 g, 1.2 mmol) was added to a solution of *N*-(3-amino-4-

15 [(cyclohexylmethyl)amino]phenyl)acetamide (1.57 g, 6.0 mmol) in dichloromethane (70 mL) at 0 °C, followed by addition of trimethylacetyl chloride (0.85 mL, 0.83 g, 6.6 mmol). The resulting mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in dichloroethane (40 mL) and then divided to 8 sealed test tubes. The mixture was heated at 170°C in a Personal
 20 Chemistry SmithSynthesizer microwave instrument for 2 h. The combined reaction mixture was dissolved in EtOAc (200 mL), washed with 2N NaOH aqueous solution (2x10 mL), brine (2x10 mL) and dried over Na₂SO₄. After filtration and evaporation, the residue was purified by MPLC using EtOAc as eluent on silica gel to give the title compound as a white solid (1.42 g, 72%). ¹H NMR (400 MHz, METHANOL-D₄) δ
 25 1.24 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.70 (m, 1 H), 1.77 (m, 2 H), 2.12 (m, 1

H), 2.18 (s, 3 H), 4.45 (d, $J=7.62$ Hz, 2 H), 7.50 (m, 1 H), 7.84 (d, $J=8.98$ Hz, 1 H), 8.43 (d, $J=1.95$ Hz, 1 H); MS (ESI) ($M+H$)⁺: 328.2.

Step F. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-acetamide

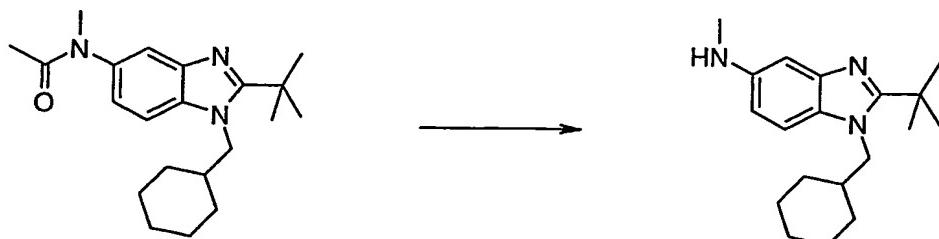
5



Sodium hydride (60%, 201.5 mg, 5.04 mmol) was added to a solution of *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide (549.8 mg, 1.68 mmol) in THF (50 mL) at 0 °C. Stirring for 1h, MeI (0.31 mL, 715.4 mg,

10 5.04 mmol) was added. The mixture was stirred overnight at room temperature, quenched with saturated NaHCO₃ (5 mL), and extracted with EtOAc (3x20 mL). The combined organic phases were washed with saturated NaHCO₃ (20 mL), brine (20 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by MPLC using EtOAc to give 580.5 mg (100%) of the title compound as a
15 white solid. ¹H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.67 (m, 2 H), 1.69 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 1.87 (s, 3 H), 2.14 (m, 1 H), 3.30 (s, 3 H), 4.49 (d, $J=7.62$ Hz, 2 H), 7.55 (d, $J=8.40$ Hz, 1 H), 7.71 (s, 1 H), 8.00 (d, $J=8.40$ Hz, 1 H); MS (ESI) ($M+H$)⁺ 342.2.

20 **Step G. *N*-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine**



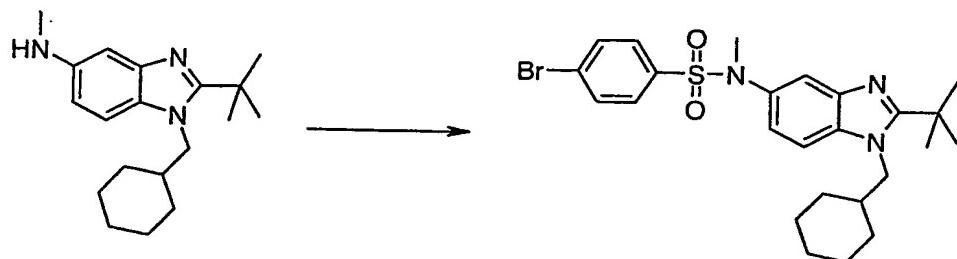
N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]acetamide (540.6 mg, 1.58 mmol) was dissolved in 20 mL of EtOH-2*N* HCl (3:2), and then

25 heated at 120°C in a Personal Chemistry SmithSynthesizer microwave instrument for

30 min. After concentration and dried in vacumn, 603.5 mg (100%) of a white solid was obtained as the title product. ^1H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.65 (m, 3 H), 1.71 (s, 9 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.17 (s, 3 H), 4.53 (d, $J=7.62$ Hz, 2 H), 7.75 (m, 1 H), 8.03 (m, 1 H), 8.17 (m, 1 H); MS (ESI) (M+H)⁺

5 300.1.

Step H. 4-Bromo-N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-N-methyl-benzenesulfonamide

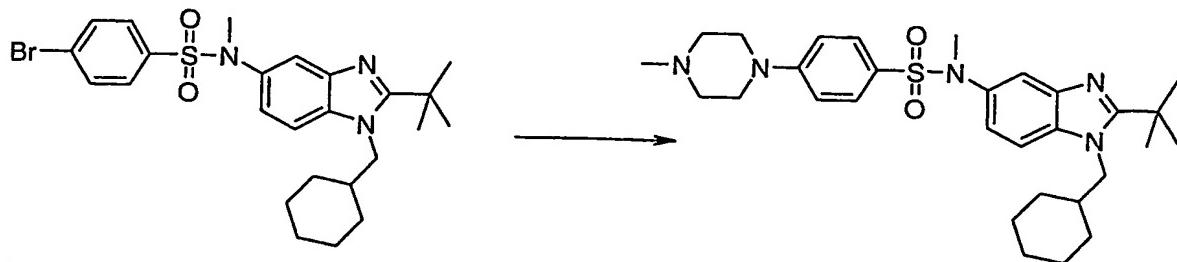


10

N-1-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-*N*-methyl-1*H*-benzimidazol-5-amine hydrogen chloride (532.2 mg, 1.39 mmol), DMAP (679.3 mg, 5.56 mmol) and 4-bromobenzene sulfonyl chloride (426.7 mg, 1.67 mmol) in MeCN (50 mL) were stirred overnight at rt. The reaction mixture was quenched with saturated NaHCO₃ (10 mL), evaporated to small volume and extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine and dried over Na₂SO₄. After evaporation of the solvent, the product was purified by MPLC using Hexanes/EtOAc (1:1) on silica to give 529.6 mg (74%) of a white solid as the title product. A small amount of the title product was converted to the corresponding TFA salt. ^1H NMR (400 MHz, METHANOL-D₄) δ 1.26 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 3.29 (s, 3 H), 4.45 (d, $J=7.62$ Hz, 2 H), 7.31(m, 1 H), 7.45 (m, 2 H), 7.53 (d, $J=1.56$ Hz, 1 H), 7.72 (m, 2 H), 7.85 (d, $J=8.98$ Hz, 1 H); MS (ESI) (M+H)⁺ 518.2.

25 Example 40

N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-methyl-1-piperazinyl)-benzenesulfonamide

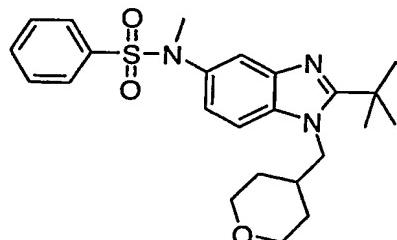


4-Bromo-N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide (50.1 mg, 0.093 mmol) and 1-methylpiperazine (0.2 mL, 180 mg, 1.79 mmol) in DMF (2 mL) were placed in a sealed tube. The mixture was

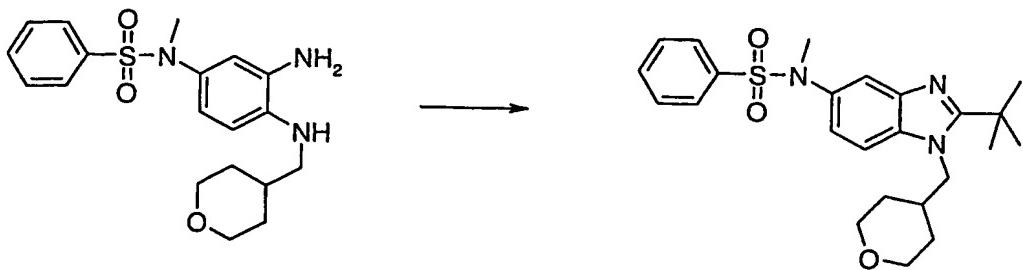
- 5 heated at 220°C in a Personal Chemistry SmithSynthesizer microwave instrument for 4 h. After evaporation, the residue was purified by reversed-phase HPLC using 15-60% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 43.73 mg (72%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.25 (m, 5 H), 1.64 (m, 2 H), 1.67 (s, 9 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.11 (m, 1 H), 2.97 (s, 3 H), 3.18 (m, 4 H), 3.24 (s, 3 H), 3.60 (m, 2 H), 4.08 (m, 2 H), 4.45 (d, J=7.62 Hz, 2 H), 7.09 (m, 2 H), 7.31 (m, 1 H), 7.46 (m, 2 H), 7.59 (d, J=1.95 Hz, 1 H), 7.83 (m, 1 H); MS (ESI) (M+H)⁺ 538.3.

Example 41

- 15 *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide



Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide

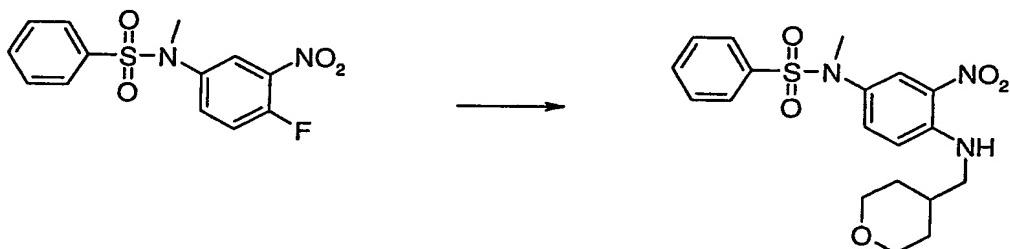


Following the procedure for Step E in Example 4, using *N*-(3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl)-*N*-methylbenzenesulfonamide (109 mg, 0.290 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride

- 5 (0.039 mL, 0.319 mmol) and DMAP (7 mg, 0.058 mmol) in 3 mL of DCM. The second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 60 mg (37%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.55 (m, 2H), 1.60 (m, 2H), 1.68 (s, 9H), 2.37 (m, 1H), 3.27 (s, 3H), 3.36 (ddd, J = 11.57, 2.64Hz, 2H), 3.93 (d, J=3.52Hz, 1H), 3.96 (m, 1H), 4.53 (d, J=7.42Hz, 2H), 7.31 (dd, J = 8.98, 1.95Hz, 1H), 7.54 (m, 5H), 7.68 (m, 1H), 7.89 (d, J = 8.98Hz, 1H); MS (ESI) (M+H)⁺ 442.3.
- 10
- 15

Step B. *N*-Methyl-*N*-(3-nitro-4-[(tetrahydro-2*H*-pyran-4-

ylmethyl)amino]phenyl}benzenesulfonamide

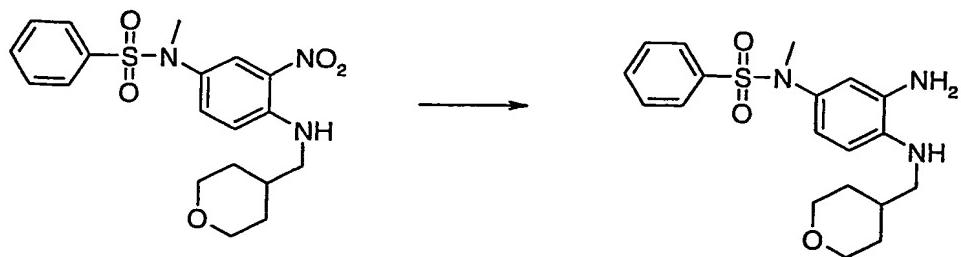


Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (100 mg, 0.322 mmol), 4-aminomethyltetrahydropyran

- 20 (45 mg, 0.386 mmol) and TEA (0.070 mL, 0.483 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using a linear gradient of 30-50% EtOAc / hexanes. Yield: 123 mg (94%); ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.44 (m,

2H), 1.74 (m, 1H), 1.77 (m, 1H), 1.96 (m, 1H), 3.13 (s, 3H), 3.23 (dd, $J = 6.74, 5.57\text{Hz}$, 2H), 3.43 (ddd, $J = 11.81, 2.15, 2\text{H}$), 4.40 (dd, $J = 11.13, 3.91\text{Hz}$, 2H), 6.84 (d, $J = 9.18\text{Hz}$, 1H), 7.49 (m, 3H), 7.61 (m, 3H), 8.21 (m, 1H).

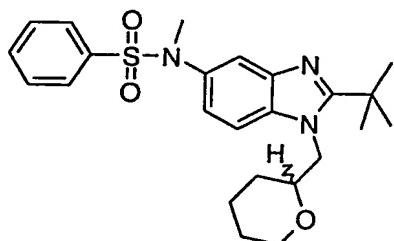
5 **Step C. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide**



- 10 Following the procedure for Step E in Example 3, using *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}benzenesulfonamide (118 mg, 0.291 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 109 mg (99%); MS (ESI) ($M+H$)⁺ 376.16.

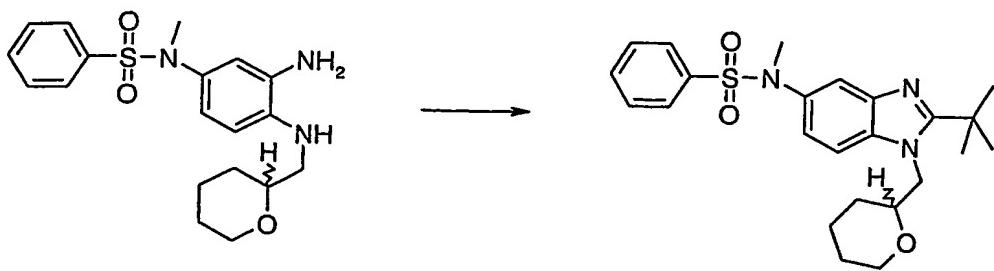
15 **Example 42**

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide**



Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-

- 20 ***y*l]-*N*-methylbenzenesulfonamide**

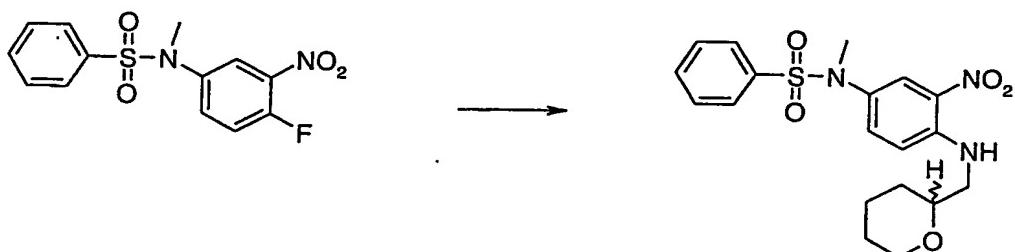


Following the procedure for Step E in Example 4, using *N*-(3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl)-*N*-methylbenzenesulfonamide (47 mg, 0.125 mmol) (for preparation, see the following steps B and C), trimethylacetyl chloride

- 5 (0.017 mL, 0.138 mmol) and DMAP (3 mg, 0.025 mmol) in 3 mL of DCM. The second step was performed in 2 mL of glacial acetic acid. The final product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 33 mg (48%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.50 (m, 2H), 1.58 (m, 3H), 1.67 (s, 9H), 1.88 (m, 1H), 1.91 (m, 1H), 3.22 (ddd, J = 11.47, 2.64 Hz, 1H), 3.27 (s, 3H), 3.85 (m, 2H), 4.65 (m, 2H), 7.29 (dd, J = 9.08, 2.05 Hz, 1H), 7.51 (d, J = 1.56 Hz, 1H), 7.54 (m, 3H), 7.68 (m, 1H), 7.87 (d, J = 8.98 Hz, 1H); MS (ESI) (M+H)⁺ = 442.3. Anal. Calcd for C₂₄H₃₁N₃O₃S+1.5 TFA + 0.1 H₂O: C, 52.78; H, 5.36; N, 6.84. Found: C, 52.83; H, 5.37; N, 6.90.

15

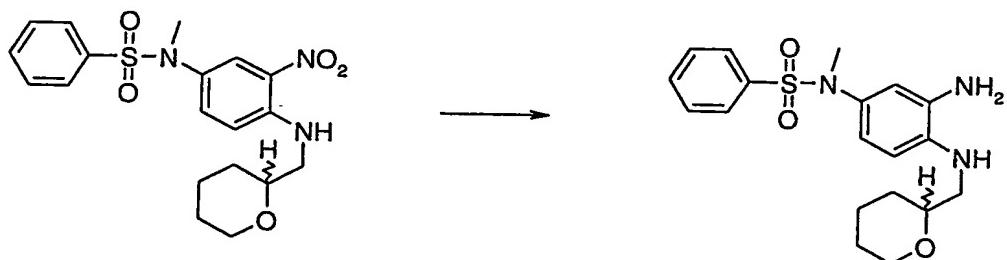
Step B. *N*-Methyl-*N*-(3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl)benzenesulfonamide



- 20 Following the procedure for Step C in Example 1, using *N*-(4-fluoro-3-nitrophenyl)-*N*-methylbenzenesulfonamide (50 mg, 0.161 mmol), 2-aminomethyltetrahydropyran hydrochloride (30 mg, 0.193 mmol) and TEA (0.056 mL, 0.403 mmol) in 3 mL of EtOH. The residue was dissolved in EtOAc and washed with 5% KHSO₄ solution, saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using first DCM and then

EtOAc as eluent. Yield: 58 mg (89%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 1.46 (m, 1H), 1.55 (d, $J = 7.03\text{Hz}$, 2H), 1.60 (m, 2H), 1.67 (m, 1H), 1.91 (m, 1H), 3.13 (s, 3H), 3.29 (m, 1H), 3.37 (m, 1H), 3.50 (ddd, $J = 11.33, 2.93\text{Hz}$, 1H), 3.62 (m, 1H), 4.06 (m, 1H), 6.83 (d, $J = 9.37\text{Hz}$, 1H), 7.46 (dd, $J = 9.37, 2.54\text{Hz}$, 1H), 7.50 (m, 2H), 7.57 (m, 2H), 7.61 (m, 1H), 8.33 (m, 1H).

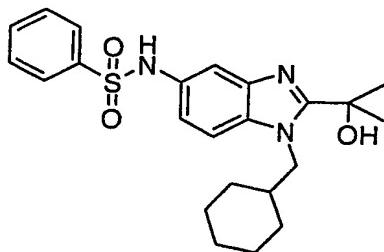
Step C. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl}-*N*-methylbenzenesulfonamide



- 10 Following the procedure for Step E in Example 3, using *N*-methyl-*N*-(3-nitro-4-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]phenyl)benzenesulfonamide (55 mg, 0.136 mmol) and a catalytic amount of 10% Pd/C in 15 mL of EtOAc. Yield: 47 mg (92%); MS (ESI) (M+H)⁺ 376.17.

15 Example 43

***N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide**



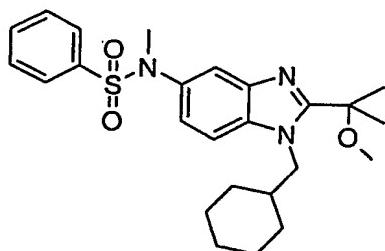
- 20 Diisopropylethylamine (291.4 mg, 2.25 mmol) was added into a solution of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}benzene sulfonamide (540.1 mg, 1.50 mmol) (for preparation, see Steps B, C and D in Example 7) and 2-hydroxy isobutyric acid (171.8 mg, 1.65 mmol) in DMF (15 mL) at 0 °C. Stirring for 20 min., HATU (684.4 mg, 1.80 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, diluted with water (100 mL), and extracted with EtOAc (2x50

mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was dissolved in acetic acid (5 mL) in a sealed tube. The solutions were heated at 140°C using a Personal Chemistry Smith Synthesizer microwave instrument for 30 min.

- 5 Upon evaporation of the solvent, the residue was diluted with EtOAc (100 mL), washed with 2N NaOH(10 mL), sat. NaCl (2x10 mL) and dried over anhydrous sodium sulphate. After filtration and evaporation, the residue was purified by MPLC (EtOAc on silica gel) to give 364.6 mg (57%) of a white solid as the title compound. Part of the product was converted to TFA salt. ^1H NMR (400 MHz, CD₃OD): δ 1.17 (m, 5 H), 1.56 (m, 2 H), 1.70 (m, 3 H), 1.76 (s, 6 H), 2.09 (m, 1 H), 4.48 (d, J=7.62 Hz, 2 H), 7.23 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 7.72 (d, J=8.98 Hz, 1 H), 7.79 (m, 2 H); MS (ESI) ($\text{M}+\text{H}$)⁺ = 428.0; Anal. Calcd for C₂₃H₂₉N₃O₃S+1.2TFA: C, 54.05; H, 5.39; N, 7.45. Found: C, 54.09; H, 5.50; N, 7.42.
- 10

15 **Example 44**

N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide



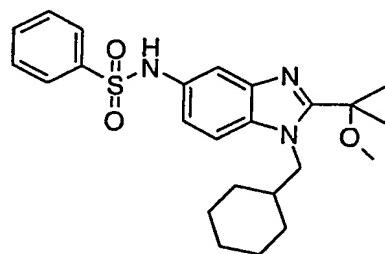
- 20 Sodium hydride (31.2 mg, 0.78 mmol) was added into a solution of *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (111.0 mg, 0.26 mmol) (for preparation, see Example 43) in THF (10 mL) at 0 °C. Stirring for 30 min., methyl iodide (145.9 mg, 1.03 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with saturated NaHCO₃ (2 mL), and extracted with EtOAc (2x50 mL). The combined organic phases were washed with NaCl (20 mL) and dried with anhydrous sodium sulphate. After filtration and concentration, the residue was purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 110.3mg (93%) of colorless syrup as the title compound, which was converted to TFA salt as a white solid. ^1H NMR (400 MHz,
- 25

CD₃OD): δ 1.21 (m, 5 H), 1.62 (m, 2 H), 1.70 (m, 1 H), 1.76 (m, 2 H), 1.79 (s, 6 H), 2.13 (m, 1 H), 3.27 (s, 3 H), 3.31 (s, 3 H), 4.46 (d, J=7.62 Hz, 2 H), 7.24 (m, 1 H), 7.47 (m, 1 H), 7.55 (m, 4 H), 7.67 (m, 1 H), 7.76 (m, 1 H); MS (ESI) (M+H)⁺ = 456.0; Anal. Calcd for C₂₅H₃₃N₃O₃S+0.8TFA+0.6H₂O: C, 57.29; H, 6.33; N, 7.54.

5 Found: C, 57.34; H, 6.31; N, 7.33.

Example 45

N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide



10

Following the same procedure in Example 44, using sodium hydride (25.0 mg, 0.63 mmol), *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide (89.3 mg, 0.21 mmol) (for preparation, see Example 43) and methyl iodide (27.4 mg, 0.19 mmol) in THF (10 mL). The desired title compound was

15 purified by MPLC (Hex/EtOAc (1:1) on silica gel) to give 34.8 mg (38%) of colorless syrup, which was converted to TFA salt as a white solid. ¹H NMR (400 MHz,

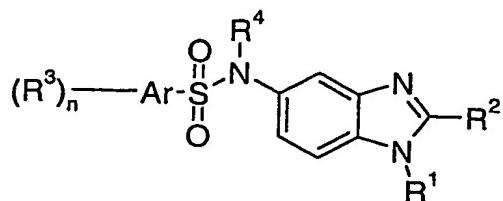
CD₃OD): δ 1.18 (m, 5 H), 1.59 (m, 2 H), 1.68 (m, 1 H), 1.74 (m, 2 H), 1.78 (s, 6 H), 2.09 (m, 1 H), 3.30 (s, 3 H), 4.42 (d, J=7.42 Hz, 2 H), 7.23 (dd, J=9.08, 2.05 Hz, 1 H), 7.47 (m, 2 H), 7.55 (m, 1 H), 7.58 (d, J=2.15 Hz, 1 H), 7.72 (d, J=9.18 Hz, 1 H), 7.80

20 (m, 2 H); MS (ESI) (M+H)⁺ = 442.0; Anal. Calcd for

C₂₄H₃₁N₃O₃S+0.9TFA+0.5H₂O: C, 56.01; H, 5.99; N, 7.60. Found: C, 55.97; H, 6.00; N, 7.47.

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:



5

I

wherein

R^1 is selected from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{R}^5\text{R}^6\text{N-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{O-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{C(=O)N(-R}^6\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{CS(=O)}_2\text{N(-R}^6\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NC(=O)N(-R}^7\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{N(R}^7\text{)-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{1-10}\text{hydrocarbyl amino}$, $\text{R}^5\text{R}^6\text{N-}$, $\text{R}^5\text{O-}$, $\text{R}^5\text{C(=O)N(-R}^6\text{)-}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{-}$, $\text{R}^5\text{CS(=O)}_2\text{N(-R}^6\text{)-}$, $\text{R}^5\text{R}^6\text{NC(=O)N(-R}^7\text{)-}$, $\text{R}^5\text{R}^6\text{NS(=O)}_2\text{N(R}^7\text{)-}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C(=O)-}$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-6}\text{heterocyclyl}$ and $\text{C}_{3-6}\text{heterocyclyl-C(=O)-}$; wherein said $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C(=O)-C}_{1-6}\text{alkyl}$, $\text{C}_{1-10}\text{hydrocarbyl amino}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C(=O)-}$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-6}\text{heterocyclyl}$ or $\text{C}_{3-6}\text{heterocyclyl-C(=O)-}$ used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-\text{NR}^5\text{R}^6$;

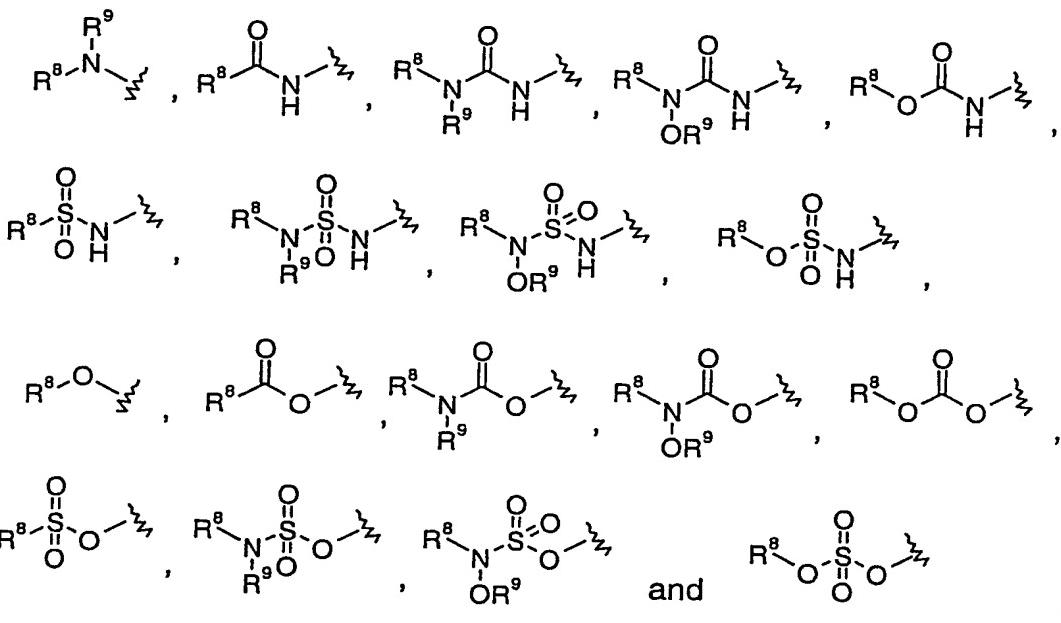
R^2 is selected from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{R}^5\text{R}^6\text{N-}$, $\text{C}_{3-5}\text{heteroaryl}$, $\text{C}_{6-10}\text{aryl}$ and $\text{C}_{3-6}\text{heterocycloalkyl}$, wherein said $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{3-8}\text{cycloalkyl}$, $\text{C}_{3-8}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-5}\text{heteroaryl}$, $\text{C}_{6-10}\text{aryl}$ or $\text{C}_{3-6}\text{heterocycloalkyl}$ used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-\text{NR}^5\text{R}^6$;

wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₁₀alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵, R⁶ or R⁷ forms a portion of a ring;

Ar is selected from C₆₋₁₀aryl and C₃₋₅heteroaryl;

5 n is selected from 0, 1, 2 and 3;

each of R³ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl optionally substituted with one or more groups selected from C₁₋₆alkyl, halogen, amino and C₁₋₆alkoxy,



10 each of R⁸ and R⁹ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, and a divalent C₁₋₆group that together with another divalent group selected from R⁸ and R⁹ forms a portion of a ring,

15 wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, or divalent C₁₋₆group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶; and

R⁴ is selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl,

20 C₃₋₁₀cycloalkyl-C₁₋₆alkyl, and C₄₋₈cycloalkenyl-C₁₋₆alkyl.

2. A compound as claimed in claim 1, wherein

- R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-10} heterocyclyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-10} heterocyclyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;
- R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , and phenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl, C_{3-5} heteroaryl, R^5R^6N- , and phenyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;
- wherein R^5 and R^6 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, and a divalent C_{1-6} alkylene that together with another divalent R^5 or R^6 and optionally a heteroatom forms a portion of a ring;
- Ar is selected from phenyl and C_{3-5} heteroaryl;
- n is selected from 0, 1 and 2;
- each of R^3 is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl optionally substituted with one or more groups selected from C_{1-6} alkyl and halogen,
-
- each of R^8 and R^9 is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl are optionally substituted by one or

more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^{10}R^{11}$; and

R^4 , R^{10} and R^{11} are independently selected from $-H$ and $C_{1-3}\text{alkyl}$.

5 3. A compound as claimed claim 1,

wherein R^1 is selected from $C_{1-6}\text{alkyl}$, $C_{2-6}\text{alkenyl}$, phenyl- $C_{1-4}\text{alkyl}$, $C_{3-10}\text{cycloalkyl-}C_{1-4}\text{alkyl}$, $C_{4-6}\text{cycloalkenyl-}C_{1-4}\text{alkyl}$, $C_{6-10}\text{aryl}$, $C_{3-10}\text{cycloalkyl}$, $C_{3-6}\text{heterocycloalkyl-}C_{1-4}\text{alkyl}$, and $C_{4-6}\text{cycloalkenyl}$, wherein said $C_{1-6}\text{alkyl}$, $C_{2-6}\text{alkenyl}$, phenyl- $C_{1-4}\text{alkyl}$, $C_{3-10}\text{cycloalkyl-}C_{1-4}\text{alkyl}$, $C_{4-6}\text{cycloalkenyl-}C_{1-4}\text{alkyl}$, $C_{6-10}\text{aryl}$, $C_{3-10}\text{cycloalkyl}$, $C_{3-6}\text{heterocycloalkyl-}C_{1-4}\text{alkyl}$, and $C_{4-6}\text{cycloalkenyl}$ used in defining R^1 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and amino;

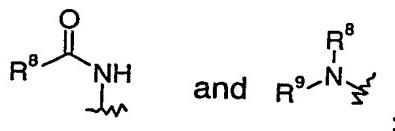
R^2 is selected from $C_{1-6}\text{alkyl}$, $C_{2-6}\text{alkenyl}$, $C_{3-6}\text{cycloalkyl}$ and $C_{3-6}\text{cycloalkyl-}C_{1-4}\text{alkyl}$, wherein said $C_{1-6}\text{alkyl}$, $C_{2-6}\text{alkenyl}$, $C_{3-6}\text{cycloalkyl}$ and $C_{3-6}\text{cycloalkyl-}C_{1-4}\text{alkyl}$

15 $C_{1-4}\text{alkyl}$ used in defining R^2 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and amino;

Ar is selected from phenyl and $C_{3-5}\text{heteroaryl}$ and

n is selected from 0, 1 and 2;

each of R^3 is independently selected from $-H$, $C_{1-3}\text{alkyl}$, $C_{3-6}\text{heterocycloalkyl}$



20 optionally substituted with one or more $C_{1-6}\text{alkyl}$,

wherein said $C_{3-6}\text{heterocycloalkyl}$ contain at least one nitrogen ring atom and the radical of $C_{3-6}\text{heterocycloalkyl}$ is located on the at least one nitrogen ring atom, and wherein each of R^8 and R^9 is independently selected from $-H$, $C_{1-6}\text{alkyl}$, morpholinyl- $C_{1-3}\text{alkyl}$, pyrrolidinyl- $C_{1-3}\text{alkyl}$, and piperidinyl- $C_{1-3}\text{alkyl}$, wherein said

25 $C_{1-6}\text{alkyl}$, morpholinyl- $C_{1-3}\text{alkyl}$, pyrrolidinyl- $C_{1-3}\text{alkyl}$, and piperidinyl- $C_{1-3}\text{alkyl}$ are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$; and

R^4 , R^5 and R^6 are independently selected from $-H$ and $C_{1-3}\text{alkyl}$.

30 4. A compound as claimed in claim 1, wherein

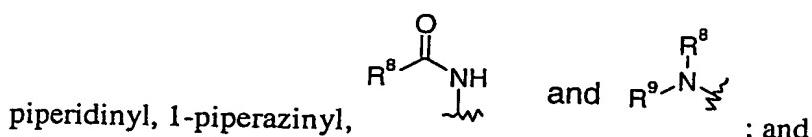
R^1 is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, cyclohexylethyl, cyclopentylethyl, tetrahydropyranyl methyl, tetrahydrofuranyl methyl, 1-piperidinylethyl, N-methyl-2-piperidinyl-methyl and benzyl;

5 R² is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-methoxy-2-propyl, 2-hydroxy-propyl, 1-cyclopropyl-ethyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-buten-1-yl, ethyl, and 2-propyl;

Ar is selected from phenyl, pyridyl, pyrimidyl, thiazolyl, thieryl, isoxazolyl, imidazolyl, and pyrazolyl:

10 n is selected from 0, 1 and 2;

each of R³ is independently selected from -H, C₁₋₃alkyl, 4-morpholinyl, 1-



wherein 4-morpholinyl, 1-piperidinyl, and 1-piperazinyl are optionally substituted with one or more methyl; and wherein each of R⁸ and R⁹ is independently selected from -H, C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl, wherein said C₁₋₃alkyl, morpholinylmethyl, pyrrolidinyl-methyl, and piperidinyl-methyl are optionally substituted by one or more groups selected from hydroxy, amino and dimethylamino.

20 5. A compound selected from:

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]thiophene-2-sulfonamide:

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylthiophene-2-sulfonamide:

25 *N*-(1-Benzyl-2-*tert*-butyl-1*H*-benzimidazol-5-yl)-*N*-methylbenzene-1,4-diol 16

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,3,5-trimethylisoxazole-4-sulfonamide.

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,2-trimethyl-1*H*-imidazole-4-sulfonamide:

30 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,1,3,5-tetramethyl-1*H*-pyrazole-4-sulfonamide;

- N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]benzene sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]benzene
5 sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-
10 benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethyl-3-butenyl)-1*H*-benzimidazol-5-yl]-
benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-
15 benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-
benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-ethyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene
sulphonamide;
- N*-[1-(cyclohexylmethyl)-2-isopropyl-1*H*-benzimidazol-5-yl]-*N*-methyl-benzene
sulphonamide;
- 20 *N*-[1-(cyclohexylmethyl)-2-(1-methylcyclopropyl)-1*H*-benzimidazol-5-yl]-*N*-
methyl-benzenesulfonamide;
- N*-[1-(cyclohexylmethyl)-2-(1-methyl-4-piperidinyl)-1*H*-benzimidazol-5-yl]-*N*-
methyl- benzenesulfonamide;
- 25 4-[1-(cyclohexylmethyl)-5-[methyl(phenylsulfonyl)amino]-1*H*-benzimidazol-2-
yl]-1,1-dimethyl- piperidinium;
- N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-
5-yl]-benzenesulfonamide;
- N*-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2-furanyl)methyl]-1*H*-benzimidazol-5-
yl]-benzenesulfonamide;
- 30 *N*-[1-(cyclobutylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-
benzenesulfonamide;
- N*-[1-(cyclopropylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-
benzenesulfonamide;

N-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl) acetamide;
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-6-morpholin-4-ylpyridine-3-sulfonamide;
5 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-nitrobenzenesulfonamide;
4-Amino-*N*-[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;
10 *N*-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)propanamide;
N-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-methylpropanamide;
15 *N*-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2,2-dimethylpropanamide;
N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(ethylamino)-*N*-methylbenzenesulfonamide;
20 *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-4-(formylamino)-*N*-methylbenzenesulfonamide;
2-Bromo-*N*-(4-{[[2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)acetamide;
25 *N*-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-pyrrolidin-1-ylacetamide;
*N*¹-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-*N*²,*N*²-dimethylglycinamide;
30 *N*-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-morpholin-4-ylacetamide;
*N*¹-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)glycinamide;
2-[(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)amino]-2-oxoethyl acetate;
N-(4-{[[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}phenyl)-2-hydroxyacetamide;

N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-morpholinyl)-benzenesulfonamide;

N-[1-(cyclohexylmethyl)-2-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(4-methyl-1-piperazinyl)-benzenesulfonamide;

5 *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbenzenesulfonamide;

10 *N*-[1-(cyclohexylmethyl)-2-(1-hydroxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide;

N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-benzenesulfonamide;

N-[1-(cyclohexylmethyl)-2-(1-methoxy-1-methylethyl)-1*H*-benzimidazol-5-yl]-benzenesulfonamide; and pharmaceutically acceptable salts thereof.

15

6. A compound according to any one of claims 1-5 for use as a medicament.

7. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the therapy of pain.

20

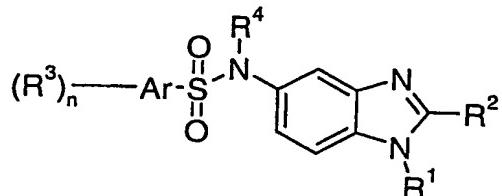
8. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of anxiety disorders.

25 9. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, cancer, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiavascular disorders.

30 10. A pharmaceutical composition comprising a compound according to any one of claims 1-5 and a pharmaceutically acceptable carrier.

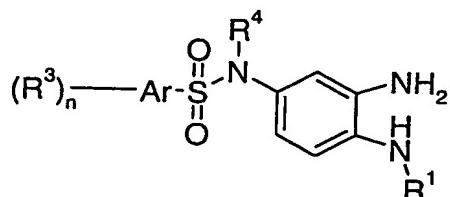
11. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-5.

5 12. A method for preparing a compound of formula I,



I

comprising the step of reacting a compound of formula II,



10

II

with a compound of $\text{R}^2\text{C}(=\text{O})\text{X}$, in the presence of a base and optionally a coupling reagent, followed by treatment with an acid;
wherein

X is selected from Cl, Br, F and OH;

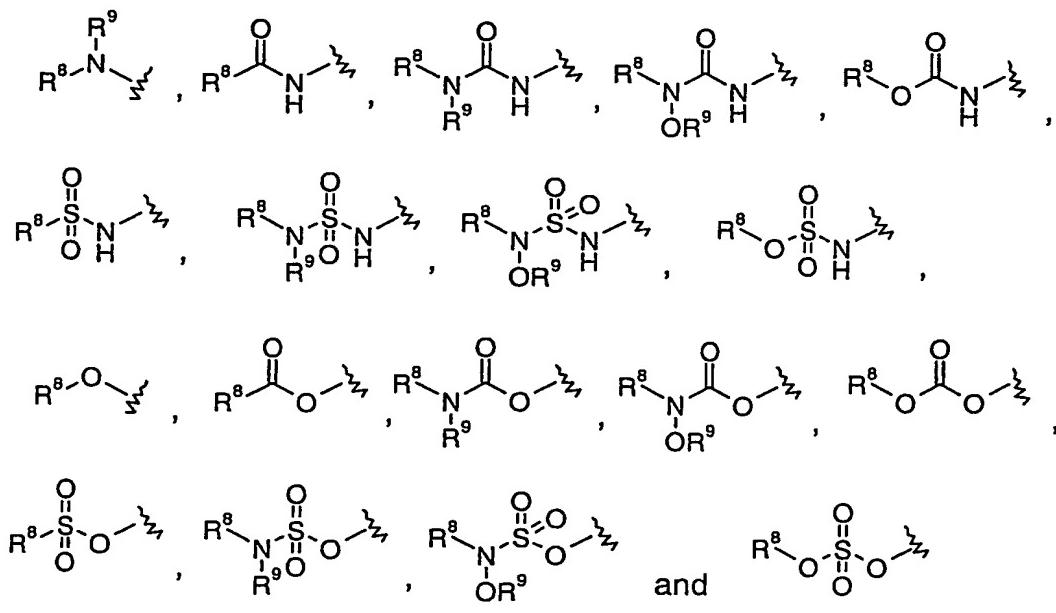
- 15 R^1 is selected from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{R}^5\text{R}^6\text{N-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{O-C}_{1-6}\text{alkyl}$, $\text{R}^5\text{C}(=\text{O})\text{N}(-\text{R}^6)-\text{C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS}(=\text{O})_2-\text{C}_{1-6}\text{alkyl}$, $\text{R}^5\text{CS}(=\text{O})_2\text{N}(-\text{R}^6)-\text{C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NC}(=\text{O})\text{N}(-\text{R}^7)-\text{C}_{1-6}\text{alkyl}$, $\text{R}^5\text{R}^6\text{NS}(=\text{O})_2\text{N}(\text{R}^7)-\text{C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$,
- 20 $\text{C}_{1-10}\text{hydrocarbyl amino}$, $\text{R}^5\text{R}^6\text{N-}$, $\text{R}^5\text{O-}$, $\text{R}^5\text{C}(=\text{O})\text{N}(-\text{R}^6)-$, $\text{R}^5\text{R}^6\text{NS}(=\text{O})_2-$, $\text{R}^5\text{CS}(=\text{O})_2\text{N}(-\text{R}^6)-$, $\text{R}^5\text{R}^6\text{NC}(=\text{O})\text{N}(-\text{R}^7)-$, $\text{R}^5\text{R}^6\text{NS}(=\text{O})_2\text{N}(\text{R}^7)-$, $\text{C}_{6-10}\text{aryl}$, $\text{C}_{6-10}\text{aryl-C}(=\text{O})-$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}(=\text{O})-$ and $\text{C}_{3-6}\text{heterocyclyl-C}(=\text{O})-$; wherein said $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkynyl}$, $\text{C}_{6-10}\text{aryl-C}_{1-6}\text{alkyl}$, $\text{C}_{6-10}\text{aryl-C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl-C}_{1-6}\text{alkyl}$, $\text{C}_{4-8}\text{cycloalkenyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{heterocyclyl-C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-10}\text{hydrocarbyl amino}$, $\text{C}_{6-10}\text{aryl}$, $\text{C}_{6-10}\text{aryl-C}(=\text{O})-$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{4-8}\text{cycloalkenyl}$, $\text{C}_{3-6}\text{heterocyclyl or}$

$C_{3\text{-}6}$ heterocyclyl-C(=O)- used in defining R^1 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

- R^2 is selected from $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}10}$ cycloalkyl, $C_{3\text{-}10}$ cycloalkyl-C $1\text{-}6$ alkyl, $C_{4\text{-}8}$ cycloalkenyl-C $1\text{-}6$ alkyl, $C_{3\text{-}6}$ heterocycloalkyl-C $1\text{-}6$ alkyl, $C_{4\text{-}8}$ cycloalkenyl, $R^5R^6N\text{-}$, $C_{3\text{-}5}$ heteroaryl, $C_{6\text{-}10}$ aryl and $C_{3\text{-}6}$ heterocycloalkyl, wherein said $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}8}$ cycloalkyl, $C_{3\text{-}8}$ cycloalkyl-C $1\text{-}6$ alkyl, $C_{4\text{-}8}$ cycloalkenyl-C $1\text{-}6$ alkyl, $C_{3\text{-}6}$ heterocycloalkyl-C $1\text{-}6$ alkyl, $C_{4\text{-}8}$ cycloalkenyl, $C_{3\text{-}6}$ heterocycloalkyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

wherein R^5 , R^6 and R^7 are independently selected from $-H$, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, and a divalent $C_{1\text{-}6}$ group that together with another divalent R^5 , R^6 or R^7 forms a portion of a ring;

- 15 Ar is selected from $C_{6\text{-}10}$ aryl and $C_{3\text{-}5}$ heteroaryl;
 n is selected from 0, 1, 2 and 3;
 each of R^3 is independently selected from $-H$, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}10}$ cycloalkyl, $C_{3\text{-}10}$ cycloalkyl-C $1\text{-}6$ alkyl, $C_{4\text{-}8}$ cycloalkenyl-C $1\text{-}6$ alkyl, $C_{3\text{-}6}$ heterocycloalkyl optionally substituted with one or more groups selected from
 20 $C_{1\text{-}6}$ alkyl, halogen, amino and $C_{1\text{-}6}$ alkoxy,

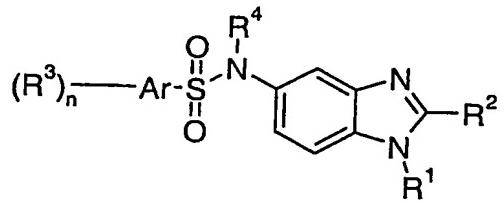


each of R⁸ and R⁹ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocycl, C₆₋₁₀aryl, C₃₋₆heterocycl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, and a divalent C₁₋₆group that together with another divalent group selected from R⁸ and R⁹ forms a portion of a ring,

- 5 wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocycl, C₆₋₁₀aryl, C₃₋₆heterocycl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, or divalent C₁₋₆group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶; and
- R⁴ is selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, and C₄₋₈cycloalkenyl-C₁₋₆alkyl.

A B S T R A C T

Compounds of formula I or pharmaceutically acceptable salts thereof:



5

wherein R^1 , R^2 , R^3 , R^4 , n and Ar are as defined in the specificationas well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

10

15